Review

Pharmacogenetics and drug-induced arrhythmias

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Abstract

Drugs are widely recognized to vary in the beneficial and undesirable effects they produce in human subjects. The understanding that variants (polymorphisms and mutations) in the human genome are common and may well modulate both disease and its response to drugs, is a critical new concept in understanding mechanisms of drug action and their variability in human subjects. Variability can arise because of variability in genes encoding molecules of drug disposition, in genes encoding molecules that drugs target, or in genes that modulate the overall activity of the complex biological systems within which drugs act. The evolving understanding of the genetic basis of variability in response to drugs used in the treatment of sudden cardiac death has important implications not only for the treatment of patients who have survived an episode, but also for helping formulate a framework for further understanding mechanisms of drug action at the genetic level. © 2001 Elsevier Science B.V. All rights reserved.

1. Introduction

It is near-axiomatic that individuals vary in their response to any drug therapy. The sources of such variability have been traditionally classified as 'pharmacokinetic' and 'pharmacodynamic'. Pharmacokinetic variability refers to variability in the conventional measures of a drug disposition: absorption, distribution, metabolism, and elimination. Inter-individual variability in these processes are well-recognized as sources of variability in the delivery of drug to, and removal of drug from important extracellular and intracellular sites of action. It is by interacting with target molecules at these sites that drugs actually exert their beneficial and detrimental effects. Even in the absence of any pharmacokinetic source of variability in drug action, patients may vary substantially in response. This is termed pharmacodynamic variability, and underlying mechanisms – which may be complex – are discussed further below.

2. Pharmacogenetics and pharmacogenomics

The notion that unusual responses to drugs might be genetically determined arose in the early part of the 20th Century when the British physician Garrod first proposed that the enzymatic pathways defective in unusual metabolic diseases (such as porphyria) might also confer unusual sensitivity to certain exogenous agents [1]. These early thoughts were reinforced by the recognition during the Second World War of development of hemolytic anemia during exposure to anti-malarial drugs among individuals (usually African–Americans) with G6PD deficiency. These pharmacodynamic examples were followed by definition of familial defects in drug metabolism as a source of variability in drug action or unusual drug effects. In the 1950s, familial pseudocholinesterase deficiency, leading to prolonged paralysis after exposure to succinylcholine, was identified [2]. The first identified common inherited trait determining drug action was that responsible for elimination by N-acetylation of drugs such as procainamide and isoniazid [3]. Slow acetylators develop a higher incidence of the lupus syndrome during procainamide therapy [4], and rapid acetylators have a higher risk for neuropathy during isoniazid therapy. The 1970s saw identification of the 'poor metabolizer' (PM) trait for substrates of the cytochrome P4502D6 (now termed CYP2D6) [5,6]. Although CYP2D6 is not abundantly expressed in liver (by

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weight), it metabolizes many drugs in common use, including some (but by no means all) antiarrhythmics, antidepressants, and beta-blockers. Description of familial CYP2D6 deficiency was followed by identification of individuals with defective metabolism of warfarin and of the anti-seizure drug mephentoin; these familial defects were not co-inherited, i.e. they reside at separate genetic loci, and since have been shown to result from DNA variants in the genes encoding CYP2C9 and CYP2C19, respectively. Importantly, these unusual responses to drug therapy were defined by astute clinical observation and family study; no specific gene defect was identified, since genes were not yet accessible for study. Thus, the field of pharmacogenetics had its start even before DNA was identified as the carrier of genetic information in human beings. Indeed, more contemporary genetic studies have revealed that ‘the’ PM phenotype can arise as a result of dozens of mutations in the CYP2D6 gene [7]. Moreover, occasional subjects with CYP2D6 gene duplication and a resultant ‘ultra-rapid’ metabolizer phenotype have been described [8].

Most drugs currently used to treat arrhythmias and other human diseases were developed at a time when the molecular basis of drug action was not well-understood. Thus, many available agents are ‘dirty’, in the sense that they target multiple molecules to produce their desirable and undesirable effects. As our understanding of the molecular basis of drug disposition and of drug interactions with their targets becomes more sophisticated, it is not only possible to refine our understanding of the mechanism of action of older drugs, but also to develop newer ones that should be ‘cleaner’. However, it is becoming clearer that the clinical actions of even ‘clean’ drugs (that interact with only a single target molecule) depend on the normal function of multiple molecules, including those involved in drug disposition as well as those modulating the drug-target interactions and the larger biologic context in which that interaction occurs. This appreciation of the multi-molecular basis of clinical drug actions in turn has led naturally to identification of the specific genes and pathways that form the basis for these molecular events. The identification of variants in multiple genes modulating drug action in turn defines a newer approach to understanding variability in drug action, pharmacogenomics. The ultimate concept, which remains to be validated, is that drug response may be predictable by defining not single variants (as in the pharmacogenetic examples) but by defining relatively large sets of variants that, together, create a pathophysiologic milieu more or less likely to result in a desirable drug effect [9–11].

Two general types of genetic variants are described: mutations and polymorphisms [12]. Mutations are generally defined as disease-associated alterations in DNA, occurring in rare (generally less than 1%) patients. Polymorphisms, on the other hand, are common variations in DNA, generally defined as occurring in greater than 1% of a selected population. Most polymorphisms occur at individual nucleotides (‘single nucleotide polymorphisms’, often referred to as ‘SNPs’). Other polymorphisms occur as repeats of dinucleotides or other groupings, or as large insertions or deletions. Some of these polymorphisms occur in coding regions of genes, and therefore may or may not change the encoded amino acid. Others occur in non-coding regions but nevertheless may modulate regulation of expression of individual genes. It is estimated that ‘the’ human genome includes ~3,000,000 SNPs.

3. The clinical pharmacology of antiarrhythmic drugs

Drug therapy of cardiac arrhythmias has been particularly instructive for pharmacokinetics, pharmacodynamics, and pharmacogenetics because the margin between drug doses and concentrations producing efficacy and those associated with toxicity (including sudden cardiac death) may be quite small. Thus, the lessons learned in the study of interindividual variability in response to antiarrhythmic drugs have had widespread applicability to other areas of drug therapy. The last five years have seen enormous advances in our understanding of rare genetically defined arrhythmia syndromes, such as the long QT syndrome and the Brugada syndrome. Such advances have not only helped understand pathogenesis in these syndromes, but have also provided a starting point for studies of the way in which variability in function or expression of these (and many other) genes can modulate response to drugs. Thus, the lines of distinction between well-defined genetic syndromes (discussed in other reviews in this issue of Cardiovascular Research) and pharmacogenetics are blurred. Moreover, this is but one manifestation of the general rule that identification of the genetic basis of disease carries with it important implications for understanding variability in drug treatment of that disease.

4. Interpreting variability in drug action in a molecular context: an example

Fig. 1 expands these theoretical considerations into a practical context for the following discussion. One drug target that has assumed some importance in the broad area of the pharmacogenetics of sudden death is the rapidly activating component of delayed rectifier current in heart, \( I_{Kr} \) [13]. This current is generated by expression of the Human Ether-a-go-go Related Gene (HERG), and modulated by at least one ancillary subunit, MiRP1 [14,15]. Mutations in HERG or MiRP1 cause the congenital long QT syndrome, and most drugs causing torsades de pointes are \( I_{Kr} \) blockers. Variability in pharmacokinetics (i.e. in absorption, distribution, metabolism, or excretion) may result in variable delivery of an \( I_{Kr} \) blocker (or metabo-
These other repolarizing currents have been described in cases of $I_{Kr}$-related torsades de pointes [16–19].

5. Drugs as a cause of sudden cardiac death: The long QT syndromes

Syncope occurring shortly after the initiation of quinidine therapy was first identified in the 1920s [20], but the electrocardiographic basis was first reported in 1964 when Seltzer and Wray [21] reported that syncope in this situation arose because of long episodes of non-sustained polymorphic ventricular tachycardia. The term torsades de pointes was actually coined two years later in connection with polymorphic VT arising in patients with advanced heart block [22]. The ensuing decades have seen expansion of a number of drugs associated with torsades de pointes. This includes not only antiarrhythmic agents, but also other drugs generally viewed as ‘non-cardiovascular’. Some drugs are associated with a high risk of torsades de pointes, particularly in the presence of risk factors defined below. For others, the association is weaker, relying on sporadic case reports or even in vitro studies to suggest a risk. In occasional cases, the presented electrocardiograms are not typical of torsades de pointes [23].

Risk factors for torsades de pointes have been identified in clinical studies. In some cases, identification of such clinical risk factors, in turn, has led to molecular studies defining the basis by which risk is increased. For other risk factors, the molecular basis is not yet well understood and further studies would thus be valuable to gain insights into the molecular basis of inter-individual variability in this unusual drug response.

Virtually all drugs that have been associated with torsades de pointes are blockers of $I_{Ks}$. Based on the precedent of the congenital long QT syndrome, one could also anticipate that drug block of $I_{Ks}$ or defective fast  

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inactivation of $I_{Na}$ might also prolong cardiac action potentials and provoke torsades de pointes, and indeed this is observed in experimental models [24]. However, no clinically used drugs are pure $I_{Kr}$ blockers or Na⁺ channel openers, so it is not known for certain that these drug mechanisms will cause torsades de pointes in patients. Interestingly, the concept of developing drugs with positive, rather than reverse, use dependence [25] led to identification of $I_{Ks}$ as an appropriate target for antiarrhythmic drug development in the early 1990s, and a number of drug companies had programs for $I_{Ks}$ blockers in place. With the identification of molecular defects in $I_{Ks}$ as the commonest cause of the congenital long QT syndrome, these drug development efforts were terminated.

5.1. Pharmacokinetics of drug-associated torsades de pointes – concentration-dependence

When the data are available, the risk of torsades de pointes increases as a function of drug dose or concentration. This is true for antiarrhythmic agents (sotalol and dofetilide) as well as cisapride, terfenadine, and astemizole, destined for non-cardiovascular indications. The one major exception appears to be quinidine, where the risk is well-recognized even after single dose and at low concentrations. In vitro studies have identified quinidine as a potent $I_{Kr}$ blocker [26], but the drug also blocks inward currents through sodium and calcium channels at high concentrations. Indeed, in vitro studies indicate that, as concentration of quinidine is increased, action potential first prolongs (reflecting $I_{Kr}$ block) and then in fact shortens, presumably reflecting block of inward currents. This multiplicity of quinidine actions likely accounts for the lack of concentration-dependence that quinidine-induced torsades de pointes. Further, it carries the very important message that variability in other electrophysiologic actions (notably calcium and sodium current block), and by extension the genes underlying those actions, can strongly modulate the likelihood and concentration dependence of $I_{Ks}$-induced torsades de pointes.

Given that the risk of torsades de pointes increases with increasing drug concentration, it follows naturally that drug interactions that increase plasma concentrations of $I_{Kr}$ blockers should increase risk of torsades de pointes. The extent to which the block of a single pathway of drug disposition alters risk for torsades de pointes depends on the importance of that pathway in the overall disposition of a specific drug. Quinidine is metabolized by multiple pathways and also undergoes renal excretion. Thus, inhibition of a single pathway of quinidine disposition is not a well-recognized risk factor for quinidine-associated torsades de pointes. On the other hand, the antihistamine terfenadine undergoes rapid and near-complete pre-systemic metabolism by the cytochrome P450A4 (CYP3A4), which is expressed in both liver and intestinal epithelium. This extensive pre-systemic metabolism results in very low (or undetectable) concentrations of parent drug and the antihistaminic effects of terfenadine administration are now recognized to reside in the active metabolite fexofenadine (marketed as Allegra). When inhibitors of CYP3A4 are administered to a patient receiving terfenadine, this pre-systemic metabolism is inhibited, and parent drug concentrations rise dramatically in plasma. Because terfenadine is a potent $I_{Kr}$ blocker (while fexofenadine is not), the risk of torsades de pointes rises dramatically with co-administration of CYP3A4 inhibitors, such as macrolide antibiotics (erythromycin, clarithromycin) and azole anti-fungal drugs (ketoconazole, itraconazole) [27].

Genetic defects resulting in absence of CYP3A4 activity might be expected to produce terfenadine-associated torsades de pointes at usual doses, in the absence of inhibitor drugs (or overdose). However, such cases are extremely unusual, in keeping with the fact that no cases of genetic defects resulting in absence of CYP3A4 activity have yet been reported. The situation for the gastric prokinetic drug cisapride is near-identical: inhibition of the drug’s extensive pre-systemic clearance by CYP3A4 is the cause of most cases of cisapride-associated torsades de pointes [28]. It should be emphasized that these spectacular clinical examples arise because the parent drugs are potent $I_{Kr}$ blockers and because there is only a single pathway determining their disposition. The situation with respect to astemizole is somewhat more complicated, as the drug undergoes metabolism by at least two pathways, and one of the active metabolites is also an $I_{Kr}$ blocker [29].

The possibility exists, and indeed is likely, that inhibition of other pathways might increase the risk of torsades de pointes for other substrates. This is probably best-developed for the anti-schizophrenic drug thioridazine (Mellaril). Thioridazine is a CYP2D6 substrate [30] and is also an $I_{Ks}$ blocker [31]. Some data suggest that the risk of thioridazine-associated torsades de pointes is increased by co-administration of CYP2D6 (but not CYP3A4) inhibitors, and the drug’s labeling was changed in mid-2000 to restrict its use, given this newer understanding of its potential risks (http://www.fda.gov/cder/ogd/rd/17923s48.PDF). The most potent CYP2D6 inhibitor identified is quinidine, which can inhibit the enzyme at dosages far lower than those used clinically (e.g. <50 mg). However, in practice, very few patients receive quinidine and thioridazine. Some antidepressants (from both tricyclic and selective serotonin re-uptake inhibitor classes) are also CYP2D6 inhibitors and are much more likely to be used in patients receiving thioridazine. Similarly, many tricyclic antidepressant drugs are themselves CYP2D6 substrates. Tricyclic antidepressant overdose is well-recognized as a cause of arrhythmias, although typically the arrhythmia is not torsades de pointes but a monomorphic tachycardia likely related to excess sodium channel block. At usual dosages, it is not clear that inhibition of a single pathway of metabolism strongly affects the likelihood of torsades de...
pointes by tricyclics, particularly as many have multiple pathways of drug disposition. Comprehensive information on substrates, inhibitors, and inducers of cytochrome P450s is presented at http://www.georgetown.edu/departments/pharmacology/davetab.html.

5.2. Pharmacodynamics of drug-associated torsades de pointes – extracellular potassium

Hypokalemia has long been recognized to prolong the QT interval (even in the absence of drug) and to increase the risk of drug-induced torsades de pointes [32,33]. Decreased [K⁺]o is now understood to decrease Ikᵢ [34] likely contributing to prolonged QT intervals by hypokalemia. This effect is termed paradoxical, since electrochemical considerations dictate that decreased [K⁺]o should increase repolarizing current. Decreased [K⁺]o increases the likelihood that Ikᵢ undergoes fast inactivation, thereby accounting for increased current [35]; decreased [K⁺]o also enhances a newly-described Ikᵢ-blocking action of extracellular sodium [36]. Importantly, we have shown that drug block of Ikᵢ, is strongly dependent on [K⁺]o; decreasing [K⁺]o from 8 to 1 mM decreased the concentration of quinidine or dofetilide to block 50% of Ikᵢ by 10–40 fold [26]. This finding likely contributes to the markedly enhanced risk of drug-induced torsades de pointes with hypokalemia.

5.3. Other risk factors

Other risk factors for torsades de pointes have been identified, but the molecular basis whereby they increase risk are not well-understood. These include female gender [37], rapid drug administration by the intravenous route [38], recent conversion from atrial fibrillation [39], the presence of congestive heart failure or cardiac hypertrophy, hypomagnesemia, and prolonged baseline QT interval (including patients with unrecognized congenital long QT syndrome) [40,41]. It seems reasonable to postulate that these risk factors act to reduce net repolarizing current (whether through Ikᵢ or other currents) thereby reducing what we have previously termed ‘repolarization reserve’. The concept is that multiple ion currents contribute to normal repolarization, and it is likely that in many patients reduction in one of these redundant mechanisms will not cause torsades de pointes. Most patients have multiple risk factors, implying that each one contributes to reduction of repolarizing current, and then superimposition of challenge by an Ikᵢ-blocker results in failure of repolarization and torsades de pointes. It is in this context that one can thus best understand how patients may carry ‘subclinical’ long QT syndrome that only becomes manifest on drug exposure. The extent to which this phenomenon underlies risk for drug-associated torsades de pointes is not yet known. In addition to sporadic cases of mutation presenting in this fashion [17,18], we and others have identified two poly-morphisms, each occurring in 1–2% of the general population (one in MinK, one in MiRP1), that appear to increase the likelihood of drug-induced torsades de pointes [15,16,19].

6. Molecular markers of drug toxicity – QT interval prolongation and the drug development process

The examples of terfenadine and cisapride (and other drugs such as terodiline, halofantrine, lidoflazine, bepridil, and ketanserin) that caused torsades de pointes during the development process, or after drug marketing, has created a problem in the area of drug regulation. Specifically, a number of new drug entities, targeted for non-cardiovascular indications, can be shown to prolong the QT interval to a small extent. Further, many of these new drug entities also block Ikᵢ, in vitro test systems. If a pre-clinical drug development program, typically involving several thousand patients, identifies subjects with torsades de pointes, then the risk is judged relatively large, and the drug is unlikely to be marketed. However, if the risk of torsades de pointes is small (e.g., <1/10,000), then a typical drug development program may not identify any cases whatsoever. In this case, further development and marketing presents a particular problem for the drug industry and for drug regulators. On the one hand, the risk of torsades de pointes may be very small, or even non-existent, depending on the size of the preclinical ‘signal’ in terms of QT prolongation and/or Ikᵢ block. On the other hand, there may be a substantial risk that is simply not uncovered by a reasonable pre-marketing program.

Regulators have become aware of this problem, and are now regularly requesting relatively detailed QT interval and other evaluations (e.g. multiple ECGs) during drug development (http://www.eudra.org/humandocs/PDFs/SWP/098696en.pdf). In industry, there appears to be greater sensitivity to Ikᵢ block as a marker for potential adverse drug effects. In practice, these issues are being worked out on a case by case basis, and require consideration of not only the risks of torsades de pointes conferred by an individual drug, but also potential benefits, particularly with respect to alternate forms of therapy that may be available; these issues are discussed in further detail in a recent Policy Conference summary [42]. These debates have most recently occurred over new antibiotics and new antipsychotic drugs. Importantly, the use of HERG block as a potential (and as yet unvalidated) model for drug toxicity is a non-specific example of the more general problem of using an increasing understanding of the molecular basis of drug action to predict drug toxicity. It seems likely that the regulatory and industrial response to the QT/Ikᵢ issue will lay the groundwork for subsequent responses to new molecular or genetic markers for other forms of drug toxicity (e.g. hepatotoxicity or bone marrow suppression), as these are identified.
7. Other drug-induced sudden cardiac death

Defects in the cardiac sodium channel have been identified in some patients with structurally normal hearts and ‘idiopathic’ ventricular fibrillation (IVF) or the electrocardiographically distinctive variant, the Brugada syndrome. The parallels between this entity and the long QT syndrome with respect to drug challenge are interesting. Just as patients with subclinical mutations in long QT disease genes may present with normal ECGs, patients with the Brugada syndrome may have normal ECGs. In both cases, drug challenge (with a QT prolonging drug in the long QT syndrome or a sodium channel blocking drug in the IVF/Brugada syndrome) may expose the electrocardiographic phenotype [43,44]. In the long QT syndrome, the sense is that such exposure increases the risk for torsades de pointes. Much less data are available with respect to the Brugada syndrome, but exposure of the ECG phenotype by drug challenge may well increase the risk of ventricular fibrillation [45]. These considerations further emphasize the extent to which identification of the genetic basis of disease is intimately linked to the genetic basis for variability in response to drug therapy.

In vitro studies suggest that the mechanism underlying ventricular fibrillation in the Brugada syndrome is exaggerated shortening of action potential duration in epicardium versus endocardium, as a consequence of sodium channel block [46,47]. Interestingly, simulated myocardial ischemia produces very similar electrophysiologic effects to those observed with sodium channel block [48,49]. Thus, it is intriguing to think that risk for sudden cardiac death in general may be related to altered sodium channel function, which could arise through variants not only in the sodium channel gene itself, but also in any of the multiple genes that control its normal expression and targeting to the cell surface. Further, this line of reasoning suggests that the now well-recognized adverse effects of sodium channel block on sudden cardiac death, exemplified in the Cardiac Arrhythmia Suppression Trial (CAST), arose at least in part through such mechanisms. Testing the concept that some or all of the excess mortality due to sodium channel block in CAST has a genetic component would require access to DNA of patients in the study, including especially those who died. Thus, a major implication for a new understanding of the genetic basis of sudden cardiac death and its response to drugs is the imperative that genetic material be obtained, where possible, on patient entry into large clinical trials.

8. Pharmacogenetics and the treatment of sudden cardiac death

The framework for considering the variability in drug action as a cause for adverse drug effects (such as drug-induced sudden death) applies equally to prediction of drug efficacy to prevent sudden death. However, syndromes of drug-induced arrhythmias and sudden death are relatively well-recognized and their mechanisms increasingly well-understood. By contrast, the mechanisms whereby drugs act to prevent sudden death, and indeed the mechanisms whereby sudden death occurs, are much less well understood and more heterogeneous. Thus, a genetic framework for understanding variability in the therapeutic response to drug therapy targeted at prevention of sudden death is much less accessible to available approaches. With the development of large databases with well-characterized drug responses and DNA samples (with appropriate controls), may come the possibility of applying pharmacogenomic approaches to identification of sets of polymorphisms likely to predict desired drug effect. At this point, it is not possible to identify specific genetic markers that will predict a beneficial effect during drug therapy to prevent sudden death.

Drugs demonstrated to prevent sudden cardiac death in clinical trials include beta-blockers and ACE inhibitors. Polymorphisms in specific disposition pathways and in target molecules have been identified for members of both classes. Many, but certainly not all, beta blockers are CYP2D6 substrates: metoprolol, timolol, and carvedilol are prominent examples. The formal possibility, therefore, exists that ultra-rapid CYP2D6 metabolizers could be exposed to less beta blockade and protection might be greatest among patients with the PM trait. These concepts have not been validated. Common polymorphisms in the β2 adrenergic receptor gene have been identified and linked to specific outcomes during drug therapy in asthma and to prognosis in patients presenting with congestive heart failure [50,51]. Much less information is available on polymorphisms, now increasingly well recognized, in the β1 receptor. One report did suggest that certain polymorphisms were much more common among patients with dilated cardiomyopathy, but how this would impact drug therapy is not yet well-established [52].

The ACE gene includes an intronic polymorphism that involves the presence or absence (defining ‘insertion’ [I] or ‘deletion’ [D] alleles respectively) of a 250 base pair segment [53]. Subjects with the DD genotype have higher ACE levels and possibly decreased response to ACE inhibitors, compared to subjects with the II or intermediate (ID) genotypes. Whether these associations are sufficiently robust to predict individual or group responses to ACE inhibitors with respect to sudden death is not known. Again, the important implication from CAST as well as the large beta blocker and ACE inhibitor trials is that the availability of DNA samples, coupled to well-characterized phenotypic information, will be crucial in future efforts to unravel these questions.

9. The future

One area in which technologies are rapidly evolving is that of polymorphism identification. It seems likely that
within the next 3–5 years we will have available not only a
well-validated human genome, but also listings of virtually
all common polymorphisms, indexed to specific genes.
These data will be used to identify polymorphisms, or
groups of polymorphisms, that predict particular diseases
or response of those diseases to drug therapies. At the level
of individual genes, it will be important to determine
whether the presence of a polymorphism alters gene
function in a measurable fashion. Indeed, we have exam-
plres in our own work of polymorphisms in cardiac ion
channels that appear to confer no phenotype in affected
individuals (even after drug challenge) and no alteration in
in vitro function. It seems reasonable that changes in some
amino acids may simply not alter protein function. On the
other hand, it may well be that our ability to define how a
specific polymorphism alters phenotype (clinically or in
vitro) are not yet sufficiently well-developed.

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References

[3] Price-Evans DA, Manley FA, McKusick VA. Genetic control of
JA. Effect of acetylator phenotype on the rate at which procainamide
induces antinuclear antibodies and the lupus syndrome. N Engl J
586.
[7] Meyer UA, Zanger UM. Molecular mechanisms of genetic poly-
morphisms of drug metabolism. Ann Rev Pharmacol Toxicol
[8] Dahl M-L, Johansson I, Bertilsson L, Ingelman-Sundberg M,
Sjoqvist F. Ultrarapid hydroxylation of debrisoquine in a Swedish
population: Analysis of the molecular genetic basis. J Pharmaco-
[13] Roden DM. Point of view: Acquired long QT syndromes and the risk
link between an inherited and an acquired cardiac arrhythmia:
KW, Keating MT, Goldstein SA. MRIP1 forms I_{Kr} potassium
channels with HERG and is associated with cardiac arrhythmia. Cell
[16] Sesti F, Abbott GW, Wei J, Murray KT, Saksena S, Schwartz PJ,
Priori SG, Roden DM, George Jr. AL, Goldstein SA. A common
polymorphism associated with antibiotic-induced cardiac arrhyth-
M, Chivoret G, Schwartz K, Cournel P, Guicheney P. KVLQI-
T C-terminal missense mutation causes a forme fruste long-QT
[18] Napolitano C, Schwartz PJ, Brown AM, Ronchetti E, Bianchi L,
Pinnavaia A, Acquaro G, Priori SG. Evidence for a cardiac ion
channel mutation underlying drug-induced QT prolongation and
life-threatening arrhythmias. J Cardiovasc Electrophysiol
Bennett PB, Norris K, Balser JR, Roden DM, George AL. KCNE1
polymorphism confers risk of drug-induced long QT syndrome by
altering kinetic properties of IKr potassium channels. Circulation
1999;100:495.
[21] Dessertenne F. La tachycardie ventriculaire a deux foyers opposes
[22] Cocco G, Stozzi C, Chu D, Pansici R. Torsades de pointes as a
[23] Shimizu W, Antzelevitch C. Effects of a K channel opener to
reduce transmural dispersion of repolarization and prevent torsade
de pointes in LQT1, LQT2, and LQT3 models of the long-QT
block of I_{Kr}: Implications for torsades de pointes and reverse


[34] Sanguinetti MC, Jurkiewicz NK. Role of external Ca\(^{2+}\) and K\(^{-}\) in gating of cardiac delayed rectifier K\(^{-}\) currents. Pflügers Arch 1992;420:180–186.


