Acquired long QT syndrome- mutations and single nucleotide polymorphisms in Japanese population

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A number of cardiovascular and non-cardiovascular drugs are known to be proarrhythmic by prolonging QT interval that is associated with a peculiar form of polymorphic ventricular tachycardia (torsade de pointes). This type of tachyarrhythmia causes syncope and often degenerates into ventricular fibrillation. The concept is now accepted as a proarrhythmia associated with the drug-induced QT prolongation. Following conditions actually aggravate this type of proarrhythmia: (1) drug overdose, (2) female gender, (3) electrolyte imbalance, and (4) bradycardia. We physicians should also pay much more attention whether prescribed drugs have a single route of elimination after degradation. Such agents can produce unexpectedly high plasma levels in the presence of the damage in drug elimination route, such as acute renal failure. The term proarrhythmia originally refers to a category of mechanistically-distinct syndromes whereby administration of an agent results in new or more frequent arrhythmias. In addition to QT prolongation, it is also used to refer other pathological conditions: digitalis intoxication and ventricular fibrillation provoked by Na channel blockers. It is ironical that antiarrhythmic agents are most proarrhythmic. Generically, a major obstacle to the widespread use of these drugs to manage cardiac arrhythmias is a relatively high incidence of these side effects, especially as drugs are considered for long-term therapy. With increasingly sophisticated drug development, hopefully, it would be possible to refine the drug specificity to the point that extra-cardiac side effects become much less common. However, the adverse effects of the drugs frequently arise from the same mechanism(s) as those whereby the drug is expected to suppress the arrhythmias. From a basic science and drug development point of view, these adverse effects and in particular the phenomenon of proarrhythmia, demonstrate the need for further refinement in our understanding of molecular targets at which the drugs are aimed. For the clinician, the problem of proarrhythmia forces a considered evaluation of the relative risk and relative benefits of therapy with a specific drug. Based on the concept, actually in the clinics, a number of large clinical trials have been conducted and encouraged the evidence-based medicine. Further understanding of the basic mechanism of proarrhythmia actually allow clinicians to avoid particularly high-risk patients and also lead to a novel way to the drug development without proarrhythmic properties. A major knowledge on the mechanism of drug-induced QT prolongation came from recent advance obtained in the study on congenital or familial long QT syndrome. It has long been recognized that relatively young families members with QT prolongation suddenly die because of arrhythmia in certain families. Three groups were classified based on their clinical features. (1) Romano-Ward syndrome was first reported condition where autosomal dominant hereditary trait was confirmed. (2) Jervell Lange-Nielsen syndrome is autosomal recessive and associated with congenital deafness. More recently, (3) Andersen’s syndrome was found to be a member of familial long QT conditions, in which long QT, periodic paralysis and various degrees of dismorphic features are associated in an autosomal dominant fashion. Since early 1990s, large-scale linkage analyses were performed in the United States, especially in Romano-Ward syndrome families, and in 1995 two genes coding cardiac ion channels were reported to be responsible in generation of the syndrome. In electrophysiological experiments, various mutations in HERG (KCNH2) and SCN5A, identified in these patients have been shown to produce either loss-of-function or gain-of-function type of functional changes in In or In, respectively, and thereby induce QT prolongation. Since then, mutations in six genes coding cardiac ion channel or their regulatory subunit proteins were noted to cause the long QT syndrome. According to the genetic cause of the disease, congenital long QT syndromes are now classified into LQT1 through 7: KCNQ1 (LQT1), KCNH2 (LQT2), KCNE1 (LQT5), KCNE2 (LQT6) and KCNH2 (Andersen’s syndrome or LQT7). A gene responsible for LQT4 was not yet identified. With gradual accumulation of knowledge on molecular basis for long QT condition, many drugs that prolong QT interval are recognized to target the In encoded by KCNH2 and therefore mimic the LQT2 type of long QT syndrome. By using a site-directed mutagenesis technique to KCNH2, Sanguinetti and his colleagues elegantly demonstrated why many drugs bind to In protein. First they compared the amino acid sequence homology around pore regions of Kv channel including KCNH2 and found several aromatic residues in S6 domain are distinct only in KCNH2. Substitution of these residues to alanine (alanine scanning) largely abolished the inhibitory actions of many drugs on KCNH2 (HERG) channels, indicating that proarrhythmias mainly results from the block of In current. In other words, if there were naturally-occurring mutations in these aromatic amino acids in S6, individuals having such mutations may be more resistant to the drug-induced proarrhythmia. Since 1995, we have conducted the genetic screening in acquired long QT patients in addition to congenital ones, and found 3 novel mutations in KCNQ1, KCNH2 and SCN5A respectively. These were associated with either (1) severe hypokalemia due to the primary aldosteronism (R259C KCNQ1), (2) advanced atrioventricular block (A490T KCNH2) and (3) administration of cisapride, a prokinetic (L1825P SCN5A). We also identified two single nucleotide polymorphisms (SNP or snip) in KCNQ1 (P448R; G643S) that may be specific among Japanese population. Based on the functional assay using a heterologous expression with COS7 cells, one of two SNPs G643S revealed relatively small but significant reduction of In currents. Since all the symptomatic probands with this SNP had any predisposing factors to onset the symptom and no family history (sporadic cases), this SNP may be a genetic variant that is more subject to other factors predisposing to the long QT condition as mentioned above. Thus, wide-scaled screenings should be designed for the search of potential SNP variants and are exclusively important to avoid unexpected effect of the agents.

References: