LEADING ARTICLE

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Is Gender a Risk Factor for Adverse Drug Reactions?

The Example of Drug-Induced Long QT Syndrome

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Abstract

Drug-induced torsade de pointes is a rare life-threatening adverse drug reaction (ADR) which is strongly influenced by gender. Drugs that prolong cardiac repolarisation include antiarrhythmics, gastrokinetics, antipsychotics, antihistamines and antibacterials. Such drugs share the potential to block cardiac voltage-gated potassium channels, particularly the rapid component (I_{Kr}) of the delayed rectifier potassium current (I_K). By doing so, such drugs usually, but not always, prolong the QT interval. Even if the electrocardiographic signs are subdued, the underlying blockade of I_{Kr} current may precipitate the occurrence of arrhythmia.

Women are perceived to be more prone to ADRs than men. Such a propensity may result from gender-associated differences in drug exposure, in the number of drugs prescribed (polypharmacy), in drug pharmacology, as well as from possible differences in the way the adverse event is perceived. A prolonged QT interval on the electrocardiogram (time that elapses from the onset of the cardiac ventricular depolarisation to the completion of its repolarisation) is associated with the occurrence of torsade de pointes and related ventricular arrhythmias. The QT interval is influenced by heart rate, autonomic nervous system, electrolyte disturbances and above all, drugs that block potassium channels.

Two-thirds of the cases of drug-induced torsade de pointes occur in women. Therefore, this adverse effect represents a perfect example of gender differences impairing women's health. Clinical and experimental studies show that female gender is associated with a longer corrected QT interval at baseline and a greater response to drugs that block I_{Kr}, both of which facilitate the emergence of arrhythmia. This results most likely from a specific regulation of ionic channel expression (potassium, calcium, etc) by sex steroids, even though nongenomic effects may play a role as well. Estrogens facilitate bradycardia-induced prolongation of the QT interval and the emergence of arrhythmia whereas androgens shorten the QT interval and blunt the QT response to drugs. Hence, underlying genetic defects of potassium channels that may be asymptomatic in normal conditions, may precipitate drug-induced arrhythmia in women more frequently than in men. Even in the presence of a drug that mildly blocks I_{Kr} and seldom prolongs the QT interval, women are still more prone to drug-induced torsade de pointes, due to their reduced cardiac 'repolarisation reserve'. This is an important aspect of I_{Kr} blockade to be aware of during the development of new drugs.

1. Female Gender and Adverse Drug Reactions

The overall death rate does not greatly differ between genders, but the incidence pattern does, partly due to the protective effects of estrogens against heart disease before menopause.[1,2] In fact, women are perceived to be more prone to adverse drug reactions (ADRs) than men,[3-5] which probably influences the incidence pattern as well. In a recent database analysis study from 2 departments of internal medicine, clinically relevant ADRs occurred in 11% of all hospitalisations and were the cause of hospital admission in 3.3% of patients.[6] The incidence of deaths possibly related to ADRs was estimated at 1.4 per 1000 over a 3-year period, in that cohort of 3624 patients. Both female gender and polypharmacy were considered risk factors.[6] Moreover, from a retrospective database analysis of 2367 ADRs gathered at a Canadian ADR clinic between 1986 to 1996, three-quarters of the ADRs reported occurred in females.[5] The drug classes associated with the most adverse effects were the anti-infectives and CNS-active drugs; skin-related reactions accounted for 49% of the ADRs.[5]

How might gender modulate the emergence and reporting of ADRs? The answer is rather complex, since each step of the pharmacology of a xenobiotic may be a possible target for the influence of gender. Thus, a female propensity to experience or report drug-related adverse effects may result from gender-related differences in drug exposure as well as in the number of drugs prescribed (polypharmacy), the drug pharmacokinetics and pharmacodynamics.[6,7] There may also be differences in the way an adverse event is perceived *per se*.[8,9] The use of gender-specific treatments may also influence the occurrence of adverse effects. Indeed, women are the only ones prescribed oral contraceptives and these agents may be associated with an increase in blood pressure, bodyweight gain, acne and an increase of the incidence of deep vein thrombosis and thromboembolism.

Polypharmacy also has a role. In a retrospective database analysis, Tran et al.[5] pointed out that polytherapy was involved in 50% of ADRs in women compared with 33% of ADRs in men. It is logical, given the fact that women live longer, that they are prone to a greater diminution of their physiological functions and hence experience reduced drug clearance. They become more fragile and subject to various diseases, hence the polypharmacy. Therefore one can expect the pharmacological actions of the drug to be more pronounced in women[10] and subsequently more ADRs will be experienced. At a comparable age in men and women, some drugs have a greater bioavailability in women for a given dose (for a comprehensive review of this topic see Harris and colleagues[7]). This is the case for β-blockers.[11] Because women have a greater exposure to metoprolol than men (higher maximum concentrations and area under the plasma concentration-time curves for a given dose), they experience a greater reduction in their exercise heart rate.[11]

The perception of and/or the reporting of an ADR may also be influenced by gender. Thus, like the nocebo effect (the experience of an unpleasant or adverse reaction while receiving placebo) that appears more frequent in patients with an 'aggressive' and competitive personality,[12] both 'pharmacodynamic' effects and incidence of ADRs appear greater in women given placebo compared with men.[8,9,13,14]

Finally, gender influences drug pharmacodynamics, i.e. at equal drug plasma concentrations, the drug response may be more pronounced in women.[7] A particularly notable example (and clinically relevant given its serious outcome) of the predominance of ADRs in women is the gender-based difference in response to drugs prolonging the cardiac repolarisation, and particularly in the risk of developing drug-induced torsade de pointes.

2. Drug-Induced Long QT Syndrome: Mechanisms

2.1 The QT Interval

The hallmark of all long QT syndromes (LQTS) is an abnormal ventricular repolarisation characterised by a prolonged QT interval on the electro-

cardiogram (ECG). The prognosis of LQTS depends on whether the syndrome is congenital or not. Congenital long QT syndrome (CLQTS) is a rare cardiac disorder in which a prolonged QT interval is associated with syncopes resulting, most of the time, in a polymorphic ventricular tachycardia, called torsade de pointes. This arrhythmia was described first by Dessertene[15] who characterised its pause-dependency and distinctive time-dependent change in electrical axis. Torsade de pointes may degenerate to ventricular fibrillation, possibly causing sudden death.

Apart from patent genetic abnormalities of cardiac ion channels that are responsible for CLQTS, prolongation of the QT interval may be the consequence of an acquired disease state or abnormalities, such as cerebral haemorrhage, electrolyte disturbances and myocardial infarction.[16-18] Finally, certain drugs may induce a LQTS. Drug-induced LQTS shares the same propensity to torsade de pointes ventricular arrhythmia as its congenital counterpart in a setting of QT prolongation. Most drugs which are associated with the occurrence of torsade de pointes and sudden death, intentionally, as in the case of antiarrhythmics, or unintentionally, as in the case of antihistamines, antibacterials and antipsychotics, block potassium channel currents and prolong the QT interval, even if sometimes only very mildly. The QT interval, which reflects ventricular repolarisation,[19] represents the summation of the action potentials of the cardiomyocytes. On the other hand, QT dispersion reflects the spatial heterogeneity of ventricular repolarisation. The latter depends on the different density and specificity of currents present in the multiple cardiac layers of cells. Probably by facilitating cardiac re-entries, prolongation of the QT interval duration and the magnitude of the QT dispersion are both positively correlated with a worsened prognosis and unexpected deaths in patients with a myocardial infarction[20] and in patients with a CLQTS.[21,22]

2.2 The Determinants of the Action Potential

The cardiac action potential results from dynamic phenomena due to the fine tuning of voltage-gated channels. The delayed rectifier potassium current (I_K) plays a particularly important role in repolarising the cardiac cell by letting the intracellular potassium out. The pharmacology of I_K, and particularly its rapid component (I_{Kr}), is now well explored, and the role of I_{Kr} during the repolarisation phase of the action potential, has been elucidated.

Drugs which block I_{Kr} prolong the action potential duration (APD), which results in an increase in the QT interval on an ECG, and enables inward currents (mainly calcium) to reactivate. Cardiac tissue then develops early after depolarisations (EADs) which are thought to trigger ventricular arrhythmias when conditions for spatial and temporal heterogeneity of refractoriness are set.[17] Several factors influence the cardiac response to potassium channel blockers and facilitate the emergence of arrhythmias. They include the autonomic nervous system, bradycardia, as APD and QT interval are inversely related to heart rate, reduction in serum level of potassium and magnesium,[23] circadian variations and pathological conditions of the myocardium itself.[16,24,25]

Most of the clinical conditions associated with a prolongation of the QT interval are well known (for review see Napolitano and colleagues[16] and Roden[18]). They comprise heart failure, left ventricular hypertrophy, myocardial ischaemia, hypothyroidism, obesity and old age.[26] Female gender appears to be an independent factor facilitating the occurrence of arrhythmias in a setting of a long QT syndrome (fig. 1). In fact, patent genetic abnormalities of potassium channels, previously undiagnosed may be revealed by drugs and affect the incidence of drug-induced torsade de pointes, particularly when non-antiarrhythmic drugs are prescribed without ECG monitoring.

Minor genetic defects of voltage-gated channels, which appear to be more frequent than previously thought and can be totally asymptomatic in the absence of drugs (defining the 'forme frustes' of the

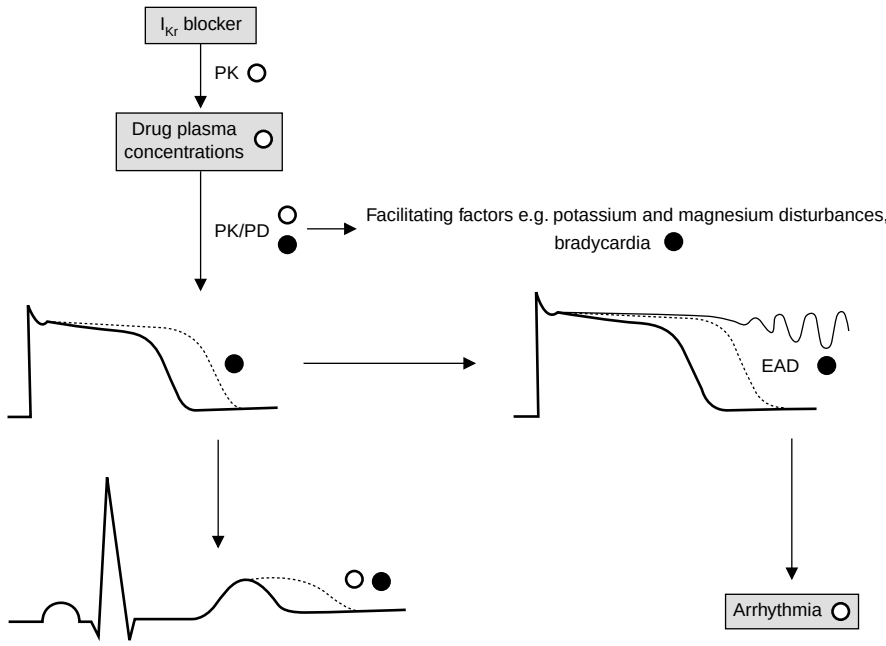

Fig. 1. Gender influences on drug-induced long QT syndrome. Plasma levels of I_{Kr} blockers may differ in males and females and with hormonal treatment[27] because of modulation in their pharmacokinetics. The blocking of I_{Kr} is responsible for the prolongation of the action potential duration that is reflected by an increase in the QT interval. During I_{kr} blockade, female gender is associated with a greater – and male with a lesser – increase in the QT interval.[28,29] The prolongation of the action potential facilitates early after depolarisations (EADs) which are held accountable for triggering torsade de pointes ventricular arrhythmias. Both are experimentally potentiated by 17β-estradiol.[30,31] Such an influence of gender is also perceptible on the pharmacodynamics and pharmacokinetics of I_K blockers, as well as resulting arrhythmias in humans.[32,33] The open circles denote points where the influence of gender and/or sex steroids has been shown clinically and the closed circles denote instances where there is only experimental evidence. **I_K** = delayed rectifier potassium current; **I_{Kr}** = rapid component of I_K; **PD** = pharmacodynamics; **PK** = pharmacokinetics.

CLQTS)[34,35] can play a role too. These 'mild mutations', including channel subunit polymorphism such as for the MIRP1 subunit, may significantly increase the sensitivity of the channel to drug inhibition.[35] Therefore, such defects may be responsible for cases of unexpected and blatant prolongation of the corrected QT (QTc) interval and/or torsade de pointes (in patients qualified as 'outliers' in clinical trials),[34,35] even if the individuals are totally asymptomatic under normal conditions.[36] This is the reason why drugs that moderately block potassium currents *in vitro* without prolonging the QTc interval in the general population (such as newer antipsychotics, the macrolide antibacterial erythromycin and some antihistamines) are still a risk for these patients, who cannot yet be identified reliably prior to treatment. Hence, a gender-dependent reduced 'repolarisation reserve'[18] affecting women may facilitate the emergence of such drug-induced torsade de pointes by unmasking more frequently these previously asymptomatic forms of congenital LQTS.

3. Female Gender as a Risk Factor for Drug-Induced Torsade de Pointes

Female gender has been associated with a longer QT interval as recorded on an ECG.[19] In fact, women seem to have a similar uncorrected QT interval to men, but a slightly faster heart rate, thus explain-

ing their longer QTc interval.[37,38] Apparently, no gender differences in QTc are present in the newborn,[39] even if a faster heart rate has been observed in a limited number of female neonates.[40] It is only around puberty that gender strongly influences the QT interval duration.[41] The QT interval then shortens in men – as it remains steady in women throughout their lifespan – to slowly return to initial values during the fifth and the sixth decade.[41] The influence of puberty on such a phenomenon led to the hypothesis that sex steroids, and androgens in particular, were the cause.

Not only is the QTc interval longer in women,[42] but the QT prolongation resulting from the administration of I_{Kr} blockers is more important too.[43,44] Subsequently, women have a greater propensity for drug–induced polymorphic ventricular arrhythmia.[45] Several clinical and experimental studies have explored this issue,[46] which suggests profound intrinsic differences of cardiac sensitivity according to gender.

3.1 Drug-Induced Long QT Syndrome in Patients with Cardiac Disorders

In the 1960s, Cramer[47] had already noticed in Scandinavia that quinidine-associated syncopes were more frequent in female patients. But it was not until 1993 that Makkar et al.[48] evaluated the pro-arrhythmogenicity of antiarrhythmic drugs using meta-analysis. Out of the 332 cases of torsade de pointes obtained from 93 articles, women accounted for 70% of the cases instead of the 50% expected.[48] Not only was the increased risk of arrhythmia particularly true for women with no organic disease,[48] but such a female predominance was later confirmed by the fact that women had greater QT interval prolongation and were more prone than men (about two-thirds of the cases) to develop torsade de pointes when given sotalol.[43,45]

It was evident then, that the female gender was associated with a worse prognosis in patients with cardiac disease treated with antiarrhythmic drugs.[44] The cause seemed to be a longer baseline QTc, a greater response to drugs and an increased propensity for experiencing drug-induced torsade de pointes. This has raised clinical concerns especially in cardiology. A task force of the American Heart Association concluded that outpatient initiation of an antiarrhythmic therapy for atrial fibrillation was a 'reasonable' approach for patients with no heart disease and a normal ECG.[49] However, some clinicians still feel that monitoring the onset of antiarrhythmic therapy for 48 hours in a hospital setting is a safer approach in women.[50]

3.2 Female Gender is an Independent Risk Factor: the Case of Non-Cardiac Drugs

Because of a possible cardiac bias affecting those results, further studies have been undertaken. Macrolide antibacterials belong to a totally different class of drugs in the non-cardiospecific domain of prescription. However, a similar propensity of for cardiac ADRs in women has been found with such drugs (two-thirds of the cases).[32] Cardiac-related adverse effects, torsade de pointes and sudden deaths were overrepresented in women treated with erythromycin lactobionate between 1984 and 1996, compared with men, although: (i) the number of prescriptions (over 1 million) were well balanced according to the gender; and (ii) the patients had no special cardiac conditions.[32] Another non-cardiac drug, the antimalarial halofantrine recently confirmed this phenomenon.[51] Among the halofantrine-related cardiovascular events reported to the US Food and Drug Administration, two-thirds occurred in women.[51] The similarity between these 2 drugs is that they both block I_{Kr} (even though they may not always have profound effects on the QT interval). Other reports have implicated new classes of drug such as antipsychotics and antihistamines (table I). One can therefore reasonably extend the notion of a 'risk factor' associated to female gender with most of the drugs that significantly block I_{Kr} and/or prolong the QT duration.

Table I. A representative list of drugs that prolong the QT interval and/or induce torsade de pointes with substantial evidence for a gender difference (when mentioned) [modified from http://www.torsades.org[52] with permission]

Class of drugs	QT prolongation and/or torsade de pointes	Females > males
Antiarrhythmics	Amiodarone	Yes
	Bepridil	Yes
	Disopyramide	Yes
	Ibutilide	Yes
	Quinidine	Yes
	Sotalol	Yes
Antidepressants	Amitriptyline	
	Desipramine	
	Doxepin	
	Haloperidol	
	Imipramine	
Anti-infectives	Clarithromycin	
	Erythromycin	Yes
	Halofantrine	Yes
	Grepafloxacin	
	Moxifloxacin	
	Pentamidine	Yes
Antihistamines	Astemizole	
	Azelastine	
	Clemastine	
	Terfenadine	Yes
Antipsychotics	Chlorpromazine	Yes
	Haloperidol	
	Quetiapine	
	Pimozide	Yes
	Thioridazine	
Other drugs	Cisapride	
	Felbamate	
	Indapamide	
	Octreotide	
	Sumatriptan	

4. Causes of the Female Predisposition to Torsade de Pointes

4.1 Gender and Pharmacokinetics

There are several reasons why women may be more prone to experience cardiac ADRs than men. Men and women have different body composition and different metabolic processes that may alter the pharmacology of a drug.[53] It has been previously shown that gender may affect drug pharmacokinetics in a way that resulting plasma concentrations and toxicity may be higher in women, than in men for similar drug doses.[7,10,54] In cases of drugs with a small therapeutic index[4] or with I_{Kr} blocking potentialities, clinically relevant adverse effects may arise,[7] as is the case with tricyclic antidepressants.[27] β-Blockers have been given as an example of drugs where gender differences affect pharmacology, resulting in higher concentrations of such agents in women.[11] This could also explain the relative protection against sudden death that benefit women treated with β-blockers.[55]

If pharmacokinetics may be influenced by gender, the modulation exerted by gender on a drug's pharmacodynamics is undoubtedly more important to consider.[56] Thus, for equal serum concentrations, the concentration-effect relationship between quinidine (whether free or bound) and QTc prolongation is much steeper in women than in men,[33] even though the baseline QTc of the female volunteers is longer than that of males. This is a clear indication that there is a fundamental difference in the way heart responds to quinidine according to the gender of the recipient.

4.2 Which Targets are Influenced by Gender?

Although the magnitude of the propensity for women to experience cardiac ADRs has been assessed,[43,57] the mechanisms and hormones implicated are still debated. In the case of CLQTS,[58,59] as well as in the case of erythromycin-induced cardiac ADRs,[32] the strong under-representation of males of sexual maturity leads to the possibility of a prominent and protective role for androgens in the prevention of QT-related cardiac ADRs. Furthermore, hormonal treatment of postmenopausal women does not seem to profoundly change their cardiac repolarisation[60] (and progesterone may even promote supraventricular tachycardia[61]).

4.2.1 Role of Androgens

Experimentally, hearts from female rabbits that have been chronically administered androgens have a blunted QT response when challenged with quinidine, and a lesser lengthening of the cardiac action potential during bradycardia, compared with either

placebo- or estradiol-treated rabbit hearts.[28,30] The results from these experiments reflect the gender differences inherent to bradycardia-induced QT prolongation of normal rabbit isolated hearts: female hearts display a greater QT prolongation with longer pacing cycle lengths.[29]

4.2.2 Role of 17β-Estradiol

It seems that sex steroids have dual effects and both estrogens and androgens account for gender differences observed in drug-induced[28,30] and probably CLQTS (fig. 1). If androgens experimentally blunt the QT response in isolated rabbit hearts, 17β-estradiol facilitates the occurrence of EADs in cardiomyocytes challenged with I_{Kr} blockers.[30] Hence, when coadministered with cisapride, which is a gastrokinetic drug and a potent I_{Kr} blocker, estradiol triggers more EADs. It also precipitates torsade de pointes in dogs, compared with sole administration of cisapride.[31]

4.2.3 Molecular Targets

A main feature associated with the modulation of the cardiac repolarisation process by gender is that the density of potassium channels in isolated cardiomyocytes differs according to the gender of the animal used in the experiment. Thus, a longer QT interval in female rabbit hearts is associated with a smaller density of I_{Kr}, inward rectifier potassium current (I_{K1})[29] and transient outward potassium currents (I_{to}).[62] Furthermore, in the cardiac papillary muscle of ovariectomised female rabbits treated with androgens, the APD30%, (which is strongly dependent on calcium influx) is shortened compared with placebo- and estradiol-treated rabbits.[30] More outward (repolarising) potassium currents and less inward (depolarising) calcium conductances in male hearts can be accountable for the shorter QT duration observed in males. Conversely, a smaller density of I_{Kr} currents in females can explain the greater QT duration at baseline, and prolongation resulting from I_{Kr} blockade (fig. 1). Human data have not yet confirmed these experiments, but in such a field these data are ethically difficult to obtain.

By which mechanisms do androgens and estrogens influence the channel regulation? Little information is available to support either genomic[28] or non-genomic[63] cardiac effects of sex steroids. When administered at physiological concentrations, sex steroids induce changes in channel subunit mRNA in target organs. This change can be rapid (less than 3 hours), like *in uteri* of ovariectomised rats.[64] Evidence from experimental studies has long indicated the presence of nuclear receptors in cardiomyocytes for estrogens and androgens.[65] Rabbit experiments have shown that KCNEI and KCNA5 mRNAs could be downregulated by sex steroids.[28] However, experimental evidence also raises the possibility of non-genomic pathways acutely modulating potassium currents.[31,66] Thus, an injection of 17β-estradiol precipitates ventricular arrhythmia in dogs, when coadministered with cisapride.[31] Likewise, estradiol potentiates the lidocaine (lignocaine)-induced depression of cardiac excitability[67] and the anti-estrogen/partial agonist drug tamoxifen blocks the native I_{Kr} current in a range of concentrations that is therapeutically relevant.[68] The rapid response in those cases suggest a non-genomic rather than genomic effect on voltage-gated channels.

The role of other hormones (i.e. progesterone[69]) and other currents [i.e. voltage-dependent sodium current (I_{Na}) or L type voltage-dependent sodium current (I_{Ca})] has yet to be thoroughly explored.[70,71]

5. Gender, QT-RR Relationship and Corrected QT Interval Changes

The higher incidence of polymorphic ventricular tachycardia in women with drug-induced LQTS is somehow related to a longer QTc interval. This parameter, highly dependent on its correction factor,[72] should be seen as a dynamic parameter modulated by the heart rate, but also by the autonomic nervous system.[24] If a longer QTc interval in women is solely a result of a correction factor in the presence of a faster heart rate,[37,38] a more global approach than QTc interval measurement, such as the QT-RR relationship, may be more relevant. It has been suggested that an abnormal adaptation of the QT interval to heart rate is related to an increased risk of cardiac events in patients with

a CLQTS.[24,73] In these patients, the QT-RR relationship is steeper compared with controls.[74-76] This is also the case in drug-induced LQTS, when patients are treated with drugs that prolong the QT interval, such as dofetilide[77] or sotalol.[78] A similar exacerbated QT-RR adaptation has already been noticed in women compared with men,[79] whose QT interval adaptation to heart rate differs significantly. This has been confirmed in young female volunteers without any cardiac abnormalities who have a steeper slope of linear regression of their QT values against the corresponding RR interval.[80] Murine[81] as well as rabbit models[29,82] display a similar gender difference, which may facilitate further experimental studies. A greater slope of the QT-RR relationship basically means that the QT interval lengthens to a greater extent during bradycardia (which is a risk factor for torsade de pointes). This underlines the respective roles played by estrogens and androgens in bradycardia-induced QT prolongation, as mentioned in section 4.2. This is also probably related to the fact that in humans, a pause almost always precedes the onset of a typical torsade de pointes arrhythmia.[15] The subsequent greater APD following the pause may facilitate the emergence of EADs and precipitate arrhythmias. Even if these elements have shed a new light on the QT-RR adaptation, further studies are needed to confirm an eventual clinical predictive value.

6. Conclusion

Women are more prone to experiencing drug-induced adverse effects. Some of the reasons for this are the greater degree of polypharmacy, the increased bioavailability of drugs and a greater sensitivity of their target organs. Drug-induced LQTS with its associated torsade de pointes represents a particularly interesting model of female gender as a risk factor for adverse effects. Even though a lower population-based incidence of sudden death in women may relate to the greater prevalence of coronary artery disease in men,[83] gender differences affect the incidence of arrhythmias and sudden death in women treated with I_{Kr} blockers. Since the work of Bazett,[19] a longer duration of the QTc interval has consistently been reported in women.[19,41,84] Indeed, women are at increased risk for severe cardiac adverse events such as torsade de pointes in drug-induced[32,43] and congenital LQTS.[59] Both androgens, by blunting the drug effects on the heart repolarisation, and estrogens, by facilitating arrhythmias, influence such an outcome. Therefore, drugs blocking potassium currents should be cautiously administered in women at risk of developing cardiac arrhythmias (for example, women with hypokalaemia or bradycardia) and only after carefully weighing up the risks and benefits of treatment.

Study of gender specificity should also be a goal of preclinical and clinical development of drugs potentially prolonging the QT interval. Finally, a female propensity to cardiac ADRs such as palpitations, ventricular arrhythmias, and syncope should raise concern about I_{Kr} blockade as a possible reason, particularly during a new drug development.

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