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Editorial Open Access

Importance of Gender Effect in Cardiovascular Pharmacology

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Introduction

Cardiovascular Disease (CVD) including stroke is the leading cause of death and disability worldwide [1] and an enormous economic burden to our societies [2]. The total direct and indirect cost in the US alone for treatment of CVD (hospitalization, drugs, home healthcare, etc.) and loss of productivity and morbidity is estimated at close to $315 billion US per year [3]. Thus prevention by improving diagnosis and drug treatment strategies could provide a huge saving for the health care cost worldwide.

The importance of gender effect in the management of CVD has long been recognized such that mortality and morbidity are higher in women than men [4]. Compared to men, women tend to develop significant CVD later in life, but their prognosis are considerably poorer and it is now the leading cause of death in elderly women [5]. Clinically women have a higher resting heart rate and longer QT interval which increase their risk for drug-induced Torsades de Pointes (TdP) [6]. Higher mortality rate is also observed in women recovering from an acute myocardial infarction [7]. It is also known that hypertension risk increases with age which is more prevalent in women and may be attributed to loss of artery elasticity more commonly occurred in women than in men [8]. Women are also more prone to increased plasma triglyceride concentrations particularly in those with low concentration of High Density of Lipoproteins (HDL) [9]. While the exact mechanism for the gender difference is not known, it may be related to gender specific risk factors such as menopause, use of hormonal replacement therapy, psychosocial factors and perhaps also many others etc. [10].

In addition to an inherent gender difference in clinical manifestation of CVD, pharmacokinetics and pharmacodynamics of many CV drugs are also known to be affected by gender [11]. Apart from differences in body mass composition which affect drug distribution in the body such that larger volume of distribution and faster clearance for most medications often occurs in men compared to women. On the other hand, a greater body fat composition in women (until older ages) may increase distribution volume for lipophilic drugs [12]. There are also differences in drug metabolism depending on the type of metabolic enzymes involved. For examples, drugs metabolized by Phase I metabolism (oxidation, reduction, and hydrolysis via cytochrome P450's 1A, 2D6, 2E1), Phase II conjugative metabolism (conjugation via glucuronyl transferase, methyl transferase) and by combined oxidative and conjugation processes are usually cleared faster in men compared to women (mg/kg basis). Metabolism by CYP2C9, CYP2C19, and N-acetyltransferase, appears to be similar in men and women. In contrast, clearance of many substrates of CYP3As is faster in women compared to men [13]. Thus in theory the difference in size between men and women means translating these results to dosage should include at least an adjustment for body size. Unfortunately, this is not a standard in clinical practice.

Over the years there are well documented examples of gender differences in specific CV drug therapy which are highlighted below:

Statins

It is known statins decrease cardiovascular events and all-cause mortality in both women and men. However, the risk of developing myalgia and other forms of myopathy is significantly higher in women who are also more likely to discontinue the statin therapy [14]. In fact female gender is one of the major risk factors that predispose patients to myopathy [15]. Thus women receive statins may be more prone to drug interactions that could result in serious adverse events.

ACE inhibitors

Angiotensin Converting Enzyme inhibitors (ACEis) are effective to manage hypertension in patients with Heart Failure (HF) and Left Ventricular (LV) systolic dysfunction, and reduce all-cause mortality in both men and women. However these agents are less effective reducing mortality in women with asymptomatic LV dysfunction [16]. In addition, side effects of ACEis such as coughing are reportedly more frequent in the female population [17].

Beta-blockers

Although the effectiveness of beta-blockers are similar in both women and men with hypertension and stable heart failure, plasma concentration of beta-blockers such as propranolol and metoprolol are found higher in women than in men [18] which could explain the frequent reports of greater drug toxicity in women [19].

Calcium antagonists

Calcium antagonists are highly effective for hypertension. It has been shown after oral dose of verapamil, women has increased oral bioavailability and decreased clearance compared to men resulting in a greater reduction in blood pressure [20]. In addition, there is evidence to suggest the blood pressure response to calcium antagonist as shown for amlodipine is more sensitive in women [21]. Thus dosage reduction may be necessary for women taking calcium antagonists [22].

Aspirin

Aspirin is an anti-platelet agent which can significantly reduce the risk of myocardial infarction in men but is apparently ineffective in women for primary prevention. On the other hand, it is effective in women for preventing stroke occurrence in women, but not in men. The gender difference could be attributed to both gender dependent

pharmacokinetic and pharmacodynamic factors [23], as well as affected by estrogen and hormone replacement therapy which can decrease platelet reactivity [24] resulting in greater cardiovascular benefits in women. Future studies are clearly needed to determine the gender-specific mechanisms of platelet action and potential differences in therapeutic outcomes from anti-platelet therapy.

Antithrombotics

Antithrombotic agents are typically either anticoagulants (oral and parenteral) or fibrinoyltic agents. Anticoagulants inhibit thrombus or clot formation, while fibrinolytics break up already formed clots. These agents reduce mortality from cardiovascular events in both men and women. However, they are often associated with an increased risk of adverse bleeding in women [25]. For example, women who receive heparin for acute myocardial infarction are more likely to achieve longer activated Partial Thromboplastin Time (aPTT) than men, which also increases bleeding risk and could be associated with an increased risk of stroke, reinfarction and mortality [26].

Digoxin

Digoxin is a cardiac glycoside with positive inotropic effect which is beneficial for treatment of heart failure. Renal clearance and volume of distribution of digoxin is lower and smaller, respectively, in women compared to men which can lead to significantly higher plasma concentration [23]. These pharmacokinetic differences such as higher serum digoxin concentrations may partially explain the increased mortality rate seen in women taking digoxin for heart failure [27]. It is important to note that although the widely accepted therapeutic concentrations of serum digoxin are between 0.8-2 ng/mL in heart failure patients regardless of gender, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) recently recommended lower serum concentrations (0.5-0.9 ng/mL) for women to reduce mortality in heart failure [23].

Antiarrhythmics

Electrocardiographic and electrophysiologic differences between men and women have long been noted. Women have a higher intrinsic heart rate than men, along with a longer corrected QT interval and a shorter sinus nodal recovery time [28]. Consequently, they tend to develop severe arrhythmia more frequently on QT prolonging therapy such as with the antiarrhythmics than men [4], potentially leading to the often fatal TdP [23]. This gender-related difference is most pronounced at the onset of puberty and gradually declines with age. By age 50, there appears to be no significant difference in QT intervals between genders [29]. The gender difference may be related to the changing hormonal concentrations (e.g. progesterone) during a menstrual cycle [23]. Future studies determining the potential arrhythmogenicity of cardiovascular agents should take this factor into account when establishing the study design to ensure cardiovascular safety data are unbiased.

Summary

Women and men are inherently different physiologically and perhaps also psychologically as such we should expect a gender difference in pharmacokinetic and pharmacodynamic profiles in CV drug therapy. There are currently insufficient data to address specific gender difference from drug trials as most animal and clinical studies have been conducted almost exclusively in the male population. Thus we should advocate the importance of a gender balance when designing safety and efficacy trials because the therapeutic as well as adverse effects of many cardiovascular drugs may be significantly different between women and men. It is noteworthy there is increasing use of package inserts for a growing number of CV drugs, including simvastatin, atorvastatin, lovastatin, heparin, enoxaparin, and sotalol, which recognize gender-related differences in drug profiles and may be used to guide adjustment of loading or maintenance doses for female patients. We should also consider the practice of gender dependent factors when prescribing drugs, as more data are emerging to improve our knowledge base to balance the risk/benefit of CV drug therapy in both women and men.

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