Sex-linked Effects of Pharmacotherapy

by Abraham Simatupang

Sex-linked Effects of Pharmacotherapy

Abraham Simatupang

Department of Pharmacology and Therapy – Faculty of Medicine
Universitas Kristen Indonesia

Abstract

After rigorous pre-clinical trials on cells, organs and animals had been done to a promising active substance, it is usually followed by clinical trial which uses human. Clinical trial comprises of three phases and one trial called post-marketing surveillance and each phase has its own objectives and characteristics. Efficacy and safety are two important factors for judging and reviewing new drugs in clinical trials. In phase one, as the drug for the very first time is applied to human body, (young) men are recruited and used particularly to determine pharmacokinetics (PK) and pharmacodynamics (PD) profiles of the drug. In phase two and three the drug are tested in patients to proof the efficacy and safety of the drug. Unfortunately, in most clinical trials, especially in early development phases, women were often not substantially recruited. Therefore, women are underrepresented in clinical trials to show the efficacy and safety issues of new drugs. The backgrounds for not recruiting women in clinical trials are many, among others are due to the possibility of toxic effects on reproductive system. The teratogenicity of thalidomide in the 60s, which then was approved for anti-emesis of pregnant women, made many drug regulatory bodies strictly forbid to include women in reproductive phase to be included in clinical trial. However, when the drug is released and used in the market, it will be also prescribed for women and adverse drug reactions can emerge. Some reports show that women are more likely experience adverse events than men have been increasing. Therefore, appeals and advocacy for increasing the number of women in clinical trials have been increased recently. This article discusses the pros and cons of carrying out clinical trials in women.

Keywords: clinical trial, gender, pharmacokinetics, pharmacodynamics, efficacy, safety

Sex-linked Pharmacodynamics-Pharmacokinetics differences of Drugs' Effects

The "Thalidomide tragedy" in late 50s and early 60s was indeed a hard punch for pharmacy industry and the development of drugs. Since then

women has been excluded in most of clinical trials done between 60s until 90s, regardless of their sexual activity, sexual orientation, etc. – for fear of causing fetal harm.[1-2] But in late 90s several women organizations and activists advocated and pushed that more women should be included in clinical trials especially for drugs to treat conditions that affected women. This was followed by formulating guidance and policies by National Institute of Health (NIH) in the US for the inclusion of women in clinical trials.[1] Biological differences between men and women could also determine the pharmacokinetics and pharmacodynamics effects of certain drugs, as it is showed in many studies. [3-5]

One comprehensive study on the effect of gender in pharmacotherapy was done by Yerman, Gan and Sin. [3] They did a comprehensive literature study, comprised of 23 trials (n= 113,494 participants) on the effects of aspirin in preventing myocardial infarction (MI). It shows that despite the overall good results of aspirin compared to placebo, a total of 27% of the variation in the non-fatal MI results could be accounted for by considering the gender mix of the trials ($p = 0.017$). Trials that recruited predominantly men demonstrated the largest risk reduction in non-fatal MI (RR = 0.62, 95% CI 0.54–0.71), while trials that contained predominately women failed to demonstrate a significant risk reduction in non-fatal MI (RR = 0.87, 95% CI 0.71–1.06).

The answer to question of why the pharmacokinetics of drugs in women could show differently from men is based by the two pharmacokinetics indicators i.e. volume distribution (Vd) and clearance (Cl) which are dependent on body weight. Generally, women weigh less than men, therefore, women are more likely receiving higher doses, since dosage-finding studies usually done in men.[4]

According to Soldin et al.[5] there are at least three reasons of sex-difference with regards to adverse events that can arise from medicaments taken by women, as is suggested in Table 1 (see below).

Table 1. Suggested reasons for sex differences in adverse event reporting (Soldin, et al. 2011)[5]

Reason for sex difference	Pharmacological reason	Pharmacological factors
Women are overdosed	Pharmacokinetics	Sex differences in volume of distribution Sex differences in protein binding of drugs Sex differences in transport, phase 1, and phase 2 metabolism
Women are more sensitive	Pharmacodynamics	Sex differences in drug targets (i) receptor number (ii) receptor binding (iii) signal transduction following receptor binding

Women are prescribed multiple medications	Drug-drug interactions	Drug-drug induced alterations Pharmacokinetics Pharmacodynamics

As it is seen from Table 1, numerous pharmacological factors are intertwined which can bring difficulties for us to determine which was the main factor that would cause the adverse reactions apart from their therapeutics effects.

Pharmacokinetics factors in women

Pharmacokinetics (PK) is defined as "what body does/acts on drugs" or is about the "fate of the drugs", which actually comprises of absorption, distribution, metabolism and excretion (ADME) of the drugs. All of these factors are also, according to the recent studies, determined by sex.[4-7] Many theoretical approaches have been used to describe or predict differences of absorption of drugs between men and women, such as, women have lower organ blood flow, that may slowing the rate of absorption.[8] It has been reported that some hormones may modify gastric acid secretion, and therefore gastric pH, and additionally a slower gastric emptying time is present in females.[9-10] On distribution, it is well known that there are some differences between men and women. Women have lower average body weight, higher body fat percentage, smaller average plasma volume and lower average organ blood flow than men[11-13] One important thing to consider is the protein binding, since major protein that are responsible for binding the drugs are also influenced by sex-hormones, which fluctuate during the menstrual cycle. As a result, important distribution differences are observed.[13-14]

Metabolism is the main subject that draws a lot of attention regarding the sex-linked differences in pharmacokinetics of drugs. Metabolism consists of two reactions, named Phase I and Phase II, and both are enzymatic reactions. Phase I reactions are oxidation, reduction and hydrolysis, whereas Phase II are acetylation, sulfation, glucuronodation and methylation. The most profound oxidative enzyme in phase I is cytochrome P-450 (CYP) which also has many isozymes. It has been reported that CYP3A4 is the major isozyme of this enzymatic pathway and is responsible of the metabolism of about 50% of the current used drugs.[4] Debated results have been published concerning the activity of this enzyme. Several authors

have suggested (based on in vitro studies) that CYP3A4 activity is higher in women than in men, while CYP1A2 and CYP2D6 activity is higher in men, and no variances or conflicting results have been reported in other CYPs. Some in-vitro findings, which sometimes are not consistent with in-vivo results, showed like CYP1A2 that is responsible for metabolism of drugs including clozapine, olanzapine, theophylline and ondansetron. This isozyme is highly activated in smokers, therefore, we can predict that the concentration of afore mentioned drugs are higher in women than in men, while men usually are smokers. Other polymorphic isozyme named CYP2C9 is also responsible for metabolism of wide variety drugs like phenytoin, several non-steroidal anti-inflammatory drugs (NSAIDs, piroxicam, diclofenac, and ibuprofen) and sulfonylureas (glimepiride, glipizide and glyburide). Although this isozyme is polymorphic, but there is no gender specific difference regarding the metabolism activity, except for phenytoin, as reported by Meyer et al.[15] Carrasco-Portugal and Flores-Murrieta has compiled the differences of some important CYP isozymes as it is shown in Table 2.[4]

Regarding the excretion, glomerular filtration rate (GFR) of women is lower than men; moreover, after normalizing GFR by the body size, a 10% difference is still seen. Therefore, renal clearance may be reduced for a wide variety of drugs.[16]

Table 2. Comparative activity of different enzymatic path- ways between genders.[4]

Enzymatic pathway	Activity
CYP1A2	M > F
CYP2C9	M = F
CYP2C19	M > F, M = F, F > M*
CYP2D6	M = F
CYP2E1	M > F
CYP3A4	F > M, M = F*
UGT	M > F

M = males, F = females; *contradictory results have been published

These characteristics leads to sex-related differences in the pharmacokinetics that brings the reduction of bioavailability and therefore to a different pharmacodynamic profile. Pharmacodynamics changes can affect both the

desired therapeutic effect of a drug as well as its adverse effect profile.

As concequences of changes in PK profiles of drugs which lead to the change of effects, we sometimes have to alterate the dosage or take an extra precautions to the unwanted effects that might occur.

Table 3. Differences in Medication Effects between Women and Men[6]

Drug class	Effect	Recommendation
Aspirin	Poorer platelet inhibition and heart attack protection in women; poorer stroke prevention in men	Consider using higher dosages in women for secondary prevention after a cardiovascular event
Beta blockers	Enhanced lowering of blood pressure and heart rate when exercising in women	Monitor blood pressure and heart rate
Digoxin	Increased mortality in women	Women require a lower dosage and a lower target serum concentration of 0.8 ng per ml (1.02 nmol per L)
Opioids	Greater analgesic response in women	Men require a 30 to 40 percent greater dosage of morphine than women
Selective serotonin reuptake inhibitors	Enhanced effect in women	Preferred therapy in women in depressive symptoms
Tricyclic antidepressants	Reduced effect in women	Choose alternative with improved effectiveness in women
Typical antipsychotics	Enhanced effect in women	Lower dosage in women or increase dosage in men

Herbal medicine and conventional medicine

Use of herbal medicine has been growing for the last 20 years in Indonesia. Many pharmaceutical industries are also started to produce herbal medicines or they developed herbal medicine departments which concentrated on research and developing new preparations of herbal medicines. Usually, the pharmacy industries focus only on following the standardization and quality procedures for planting, harvesting, and manufacturing of herbal medicines required by the authorities. Furthermore, they do some clinical research to get clinical evidence for new indications that is different from the previous traditional use of the herbs. Although most of the herbal medicines are claimed safe and used only for prevention and health maintenance, however, there is still lack of clinical research or reports on the advantageous or unwanted effects of concomitant use of herbal and conventional medicine in patients with particular conditions or ailments. Therefore, there are a lot of subjects to study regarding the sex-linked differences of pharmacotherapy.

Conclusion

The pharmacokinetics and pharmacodynamics relationship in correlation with sex of many drugs are not always clear. Many contributing factors like physiological and pathological condition of the subjects are influencing this phenomenon. However, it seems that an important contribution for

observing higher levels in women is that usually doses employed in women are higher than in men when they are normalized by the body weight.

References

1. Lippman A. The Inclusion of Women in Clinical Trials: Are We Asking the Right Questions? Women and Health Protection. March, 2006. Bureau of Women's Health and Gender Analysis, Health Canada.
2. Prout MN, Fish SS. Participation of women in clinical trials of drug therapies: a context for the controversies. Medscape General Medicine. 2001; 3(4).
3. Yerman T, Gan WQ, Sin DD. The influence of gender on the effects of aspirin in preventing myocardial infarction. BMC Medicine 2007, 5:29 doi:10.1186/1741-7015-5-29.
4. Carrasco-Portugal M del Carmen, Flores-Murrieta FJ. Gender Differences in the Pharmacokinetics of Oral Drugs. Pharmacol & Pharm, 2011, 2: 31-41.
5. Soldin OP, Chung SH, Mattison DR. Sex differences in drug disposition. Review article. J Biomed. Biotech. 2011, 14 pp, doi: 10.1155/2011/187103.
6. Whitley HP, Lindsey W. Sex-Based Differences in Drug Activity. American Family Physician. 2009; 80, 11: 1254-8.
7. Margaret Ann Miller. Gender-Based Differences in the Toxicity of Pharmaceuticals—The Food and Drug Administration's Perspective. Inter. J of Toxicol. 2001; 20: 149–52.
8. Fletcher CV, Acosta EP, Strykowski JM. Gender Differences in Human Pharmacokinetics and Pharmacodynamics. J of Adolesc Health. 1994. 15, 8: 619-29.
9. Gandhi M, Aweeka F, Greenblatt RM, et al. Sex Differences in Pharmacokinetics and Pharmacodynamics. Annual Rev Pharmacol Toxicol. 2004. 44: 499-523.
10. T. Coskun, A. Sevinc, I. Tevetoglu, et al. Delayed Gastric Emptying in Conscious Male Rats Following Chronic Estrogen and Progesterone Treatment. Research in Experimental Methods. 1995.195: 49-54.
11. Beierle I, Meibohm B, Derendorf H. Gender Differences in Pharmacokinetics and Pharmacodynamics. International J Clinical Pharmacol Therapeut. 1999. 37. 11: 529-47.

12. Harris RZ, Benet LZ, Schwartz JB. Gender Effects in Pharmacokinetics and Pharmacodynamics. Drugs. 1995. 50. 2: 222-39.

13. Pleym H, Spigset O, Kharasch ED, et al. Gender Differences in Drug Effects: Implications for Anesthesiologists. Acta Anesthesiologica Scandinavia. 2003. 4. 3: 241-59.

14. Succari M, Foglietti MJ, Percheron F. Microheterogeneity of Alpha 1-Acid Glycoprotein: Variation during the Menstrual Cycle in Healthy Women, and Profile in Women Receiving Estrogen-Progestogen Treatment. Clinical Chimica Acta. 1990. 187.3: 235-41.

15. Meyer MC, Straughn AB, Mhatre RM, et al. Variability in the Bioavailability of Phenytoin Capsules in Males and Females. Pharmaceutical Research, 2001. 18, 3: 394-7.

16. Gross JL, Friedman R, Azevedo NJ, et al. Effect of Age and Sex on Glomerular Filtration Rate Measured by 51Cr-EDTA. Brazil J Medical and Biologic Res. 1992. 25, 2: 129-34.

Sex-linked Effects of Pharmacotherapy

ORIGINALITY REPORT

28%	25%	28%	12%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	file.scirp.org Internet Source	16%
2	www.illnessofhuman.com Internet Source	5%
3	etheses.saurashtrauniversity.edu Internet Source	2%
4	Miriam del Carmen Carrasco-Portugal, Francisco Javier Flores-Murrieta. "Gender Differences in the Pharmacokinetics of Oral Drugs", Pharmacology & Pharmacy, 2011 Publication	1%
5	Submitted to Higher Education Commission Pakistan Student Paper	1%
6	Submitted to 59778 Student Paper	1%
7	J Tamargo, G Rosano, T Walther, J Duarte et al. "Gender differences in the effects of cardiovascular drugs", European Heart Journal - Cardiovascular Pharmacotherapy, 2017 Publication	1%
8	jurnal.ugm.ac.id Internet Source	1%

Exclude quotes On

Exclude matches < 1%

Exclude bibliography On