PHARMACOKINETICS IN REAL LIFE: SEX AND GENDER DIFFERENCES

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ABSTRACT

Practitioners are often troubled by the lack of well characterized data on appropriate drug dosing, on effectiveness of treatment, and on drug safety for women and for women in pregnancy. We continue to struggle with how to best treat women during pregnancy and with the real life sex and gender differences in drug pharmacokinetics. This presentation looks at sex differences as a platform for considering the pharmacological status of women and how pregnancy changes that status. Specific examples of sex and gender differences in drug disposition/pharmacokinetics are discussed. The examples describe how sex-based differences influence treatment options and goals.

Key Words: *Sex differences, pharmacokinetics, pharmacodynamics, bioequivalence, drug disposition, adverse drug reactions, adverse drug events*

Practitioners are often troubled by the lack of well characterized data on appropriate drug dosing, on effectiveness of treatment, and on drug safety for women and for women in pregnancy. There have been attempts in the past decade to improve the situation by including women in clinical trials and by asking for evidence-based information about drug dosing, safety and effectiveness in women, as well as in mothers and their fetuses, and about drug effects on the placenta during the course of pregnancy. Yet we continue to struggle with how to best treat women during pregnancy and with the real life sex and gender differences in drug pharmacokinetics.

The objective of this presentation is to look at sex differences to present a platform for considering the pharmacological status of women and how pregnancy changes that status. We will review specific examples of sex and gender differences in drug disposition. As Professor Schwartz, who has written extensively on sex differences, notes in the book, *Principles of Gender-Specific Medicine*, "Women make up more than half of the population of the world … however, information regarding … treatment … fills far less than half the medical … literature."[1] This issue of sex and gender differences has recently been illustrated by the United States Food and Drug Administration (US FDA) ruling to decrease the initial recommended dose of the sedative-hypnotic, zolpidem.[2] Part of the rationale was that some patients, and particularly women, clear the drug more slowly and appear to be more susceptible to next-day drowsiness as a side effect.

Men and women differ in a range of ways as regards disease risks and processes. Sex, pregnancy and gender differences influence both drug pharmacokinetics (what the body does to the drug) and drug pharmacodynamics (what the drug does to the body). Sex-based differences consequently influence treatment options and goals. Patient management can therefore best be considered in the context of personalized medicine: ensuring the diagnosis is appropriate for the individual and that the therapeutic strategies

meet that individual's needs and address both the diagnosis and other personal factors. Along the course of treatment, monitoring determines whether the given treatment is effective and safe, and involves watchfulness for serious or common adverse events.

Physiology

There are distinct differences in physiological parameters between men and women. Data from the International Commission on Radiological Protection identifies a variety of parameters and shows the sex differences in the US population (Table 1).[3] Body mass is a visible example of a difference between the sexes. Although physical size plays a role, differences go beyond size. That is, a woman is not a small man, nor is a man a large woman. Endocrinological events, such as the onset of puberty in boys and girls, occur at different ages, produce different body compositions and variations in body fat, height and growth. Various factors come together to create the anatomic, physiologic, biochemical and endocrine differences between men and women that can influence drug disposition and response.

Taking a common example of exposure to a drug, Barquín and colleagues simulated drinking with a light meal in a social setting to determine aspects of alcohol disposition and response.[4] Fifteen minutes after drinking three 95 mL glasses of wine, almost half of the female participants had breath alcohol levels above the legal limit for driving in Europe. None of the males had levels above that limit. Over time the women's alcohol levels continued to remain higher than the men's. Only after 2 hours were all women below the legal driving limit. This is a simple example that clearly demonstrates sex differences in response to a drug.

TABLE 1 Select physiological parameters and their values for men and women

Parameter	Adult Male	Adult Female
Mass (kg)	73	60
height (cm)	176	163
Body Surface Area (m^2)	1.90	1.66
Fat (kg)	14.6	18.0
Ventilation Rate (m^3/day)	22.9	18.5
Cardiac Output (Liter/min)	6.5	5.9
Tissue Mass (g, varies with age)		
Liver	1,800	1,400
Lung	500	420
Kidneys	310	275
Fat (storage fat)	14,600	18,000
Blood Flow Rate (% Cardiac Output)		
Liver	25.5	27
Kidneys	19	17
Fat	5.0	8.5
Skeletal muscle	17	12

(Extracted from ICRP, 2002. Basic Anatomical and Physiological Data for Use in Radiological Protection Reference Values. ICRP Publication 89. Ann ICRP. 32:3-4.)

Adverse Drug Events

After determining the most appropriate treatment for a particular disease, and focusing on its effectiveness in the given situation and patient, the next concern is to monitor that treatment. Monitoring must first include making sure that the intended effect is obtained and then identifying other treatment consequences, particularly adverse events. Moore and colleagues analyzed adverse drug events reported to the US FDA between 1998 and 2005.[5] They plotted the reported numbers of serious adverse events, together with the number of outpatient prescriptions, against time over the years 1998 to 2005. They noted that serious adverse events increased 4 times faster than the rate of increase in prescriptions over the time period studied. Furthermore, they observed a sex difference in the reporting of events: 56% of reports were from females and 44% from males.

If adverse events are a concern, can we anticipate them? Are there elements to look for that would cue us to monitor particular patients more closely for adverse events? A 1998 study by Tran et al. in a Toronto hospital found "that female gender is a risk factor for the development of adverse drug reactions."[6] In 2008, Zopf and colleagues published a prospective study conducted in 2 German university hospitals.[7] All patients admitted to internal medicine were evaluated on admission for their medical history and clinical and laboratory values and were subsequently assessed for adverse drug reactions (ADRs) during the course of the study. Of the 907 patients reviewed, over one-third of them, 354, experienced 592 ADRs. The factors on admission that were predictors of ADRs included female sex, body temperature and the number of drugs administered. Being female seems to be a strong predictor of the occurrence of ADRs in hospital. What is behind this predisposition?

Evans and colleagues studied adult patient predisposition to adverse drug events reported over a 10-year period in a US tertiary teaching hospital. They published their results in a 2005 paper.[8] Their analyses included review of patient, drug and patient-type characteristics. One of the patient-specific factors related to adverse events was female sex. Of course, other factors, such as renal function, comorbidity and disease-related issues, played an expectedly strong role. The authors broke down the risk factor of sex, analyzing it against therapeutic drug class. They found that for all drug categories, except anti-infectives, women had a substantially greater risk than men for experiencing adverse events (Table 2). The female risk was also higher for all serious adverse drug events.

TABLE 2 Adverse drug reaction analysis by drug class and sex

Drug Class	% ADR	Female Odds Ratio (95% CI)
All drugs	100%	1.5 (1.4 – 1.6)
Analgesic	60%	1.7 (1.4 – 2.1)
Anti-Infectives	20%	1.2 (1.0 – 1.4)
Cardiovascular Agents	7%	1.4 (1.1 – 1.8)
Anticoagulants and fibrinolytics	4%	1.6 (1.1 – 2.3)
Severe ADEs All drugs		1.6 (1.2 – 2.2)

(Adapted from Evans RS, Lloyd JF, Stoddard GJ, Nebeker JR, Samore MH. Risk factors for adverse drug events: a 10-year analysis. Ann Pharmacother. 2005;39(7-8):1161-1168.)

The question remains as to why we see these sex differences. Sex differences in pharmacology and toxicology have been observed for many decades in animal testing. Some have argued that women have more frequent use of some prescription medications.[9,10] Tran's study found that women indeed used an average of 1.9 medications, compared to the men's average of 1.3.[6] Polypharmacy may also be a contributing factor.[11] Tran and colleagues also observed that a greater proportion of women (83%) than men (72%) consulted their physicians regularly, perhaps producing an increased reporting rate for adverse events.[6] It should also not come as a surprise that there may be some underlying biological mechanisms to support differences in adverse drug reactions,[12,13] as well as for differences in disease risk,[14-16] immune response, use of medications, and response to drugs between men and women.[17-20]

Pharmacokinetics

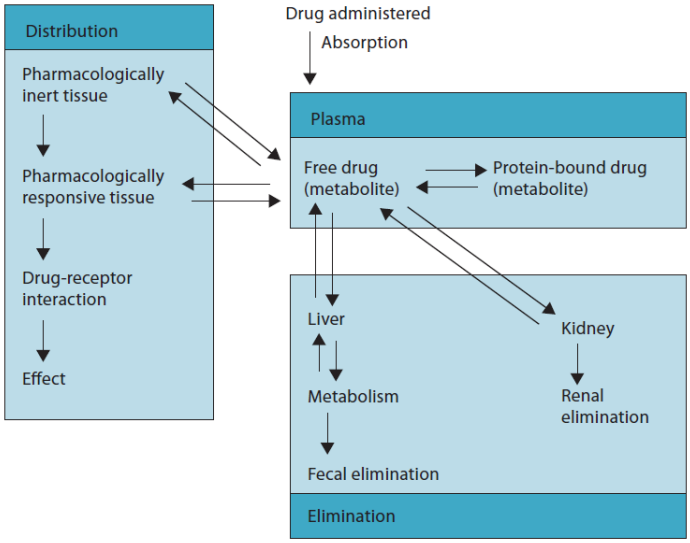
Bioavailability

Figure 1 shows the basic stages of pharmacokinetics.[9] Bioavailability, comprising drug absorption and plasma distribution, will be the first stage discussed.

In a bioequivalence study from Spain, two formulations of amlodipine were tested in normal male and female volunteers.[21] The same 10 mg oral dose resulted in a higher maximum serum concentration in women than in men, as well as a larger weight-adjusted dose, and a greater exposure, based on the area under the concentration-time curve (AUC). As expected, the effect of the drug was more pronounced in women, who experienced a significantly lower systolic blood pressure and a somewhat lower diastolic pressure. Women's heart rates were significantly higher - an expected response to the blood pressure change. We do not know whether this study identifies a simple pharmacokinetic difference, where women have a smaller body weight and volume of distribution, or whether there are other reasons for the differing responses to the drug. Given that we see differences between men and women in drug bioavailability, what factors can be causing this difference?

A number of parameters may influence drug absorption, as shown in Table 3. It is clear that men, women and pregnant women are not alike. The question is whether these differences are therapeutically relevant.

FIG. 1 Diagram of pharmacokinetic steps



(*Mattison Faye ACM, Mattison DR. Drug disposition and effect. In: Schenck-Gustafsson K, DeCola PR, Pfaff DW, Pisetsky DS, eds. Handbook of Clinical Gender Medicine. Basel: Karger, 2012:473-479.*)

TABLE 3 Physiological parameters which influence absorption.

Parameter	Physiologic Difference	Pharmacokinetic Impact
Gastric pH	acidity M > F > pregnant F	Altered absorption of acid/bases depending on specific drug ionization. In pregnancy decreased absorption of weak acid
Gastric Fluid Flow	M > F	Higher absorption in males
Intestinal Motility	M > F > pregnant F	Absorption increased in males
Gastric Emptying	M > F > pregnant F	Absorption, gastric hydrolysis increased
Dermal Hydration	Increased in pregnant F	Altered absorption in pregnant F
Dermal Thickness	M > F	Absorption decreased in males
Body Surface Area	M > pregnant F > F	Absorption increased when surface area larger
Skin Blood Flow	Increased in pregnant F	Absorption increased
Pulmonary Function*	M > pregnant F > F	Pulmonary exposure increased in males
Cardiac Output*	M > pregnant F > F	Absorption increased in males
M = male; F = female * normalized for body surface area		

(*Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143-157.*)

TABLE 4 Sex differences in body composition parameters which influence distribution.

Parameter	Physiologic Difference	Pharmacokinetic Impact
Plasma Volume	pregnant F > M > F	Decreased concentration in pregnancy
Body Mass Index (BMI)	M > F	Higher in men
Average Organ Blood Flow	Pregnant F > M > F	Higher in pregnant women
Total Body Water	M > pregnant F > F	Decreased concentration
Plasma Proteins	M, F > pregnant F*	Free concentration increases in pregnancy
Body Fat	pregnant F > F > M	Increased body burden of lipid-soluble drug in women
Cardiac Output	M > pregnant F > F	Increased rate of distribution in men
M = male; F = female * An exception is thyroxine binding globulin, which increases by 50% in pregnancy.		

(*Adapted from Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143-157.*)

Chen and colleagues evaluated 26 bioequivalence trials submitted to the US FDA's Center for Drug Evaluation and Research to determine whether women should be included in bioequivalence trials and whether dosage adjustments might be needed in women when compared to men.[23] They analysed 47 data sets for each of two parameters: the maximum drug concentration and the area under the plasma concentration vs. time curve (AUC), an indicator of drug exposure. In about one quarter of the data sets (11/47), men and women showed the same peak concentration (C_{max}) results. Three quarters of the data sets (33/47) showed that women reached a higher maximum drug concentration than men; and 3/47 data sets had men reaching a higher peak than women. Furthermore, excluding body weight as a parameter in the statistical model, 19/47 data sets had pharmacokinetic differences of 20% or more. (This 20% cut-off value was taken by the authors to indicate difference. It was the general standard accepted by

the FDA for bioequivalence studies.) Therefore, 19 studies showed a difference between men's and women's C_{max}, identifying the drugs as non-bioequivalent. Sixteen of the studies showed a statistically significant difference. Looking at the AUC data, again in about one quarter of the data sets (13/47) men and women showed the same AUCs. A little over one-half (27/47) found that women reached a higher AUC than men, and 7/47 showed men reaching a higher AUC than women. In this group of data sets, 18/47 had pharmacokinetic differences of 20% or more, of which 10 were statistically significant. Response to a drug is believed to be influenced by these two parameters-maximum drug concentration and AUC-which are initial steps in exposure to a drug and have been shown to be different in men and women.

Distribution

A range of physiological parameters that differ between men and women can influence drug distribution. These include, among others, plasma volume, body mass index, body fat, and plasma proteins.[22] In our review, we also investigated whether the use of oral contraceptives has been reported to affect plasma protein binding.[22] Table 4 outlines physiological differences among males, females, and pregnant females and how they can affect drug pharmacokinetics.

Metabolism

In a review by Meibohm and colleagues, verapamil was given as an example where differences in drug metabolism between men and women have been shown.[24] Verapamil is a calcium channel blocker that undergoes extensive first-pass metabolism by a number of cytochrome enzymes and is a substrate for P-glycoprotein. Meibohm et al. identified differences not only by sex, but also by age. As indicated by AUC, women had greater exposure to the drug than men, and elderly women showed higher drug levels and AUC than young women. Women exhibited longer increases in heart rate (as a response to decreased blood pressure) than men. The differences could be due to exposure or to exposure coupled with differences in sensitivity. Drug metabolism and transport are now additional factors which could be different in men vs. women.

Greenblatt and colleagues evaluated studies of drugs that were substrates for cytochrome P450 3A (CYP3A) to determine whether gender plays a role in their metabolism.[25] Drugs that were P-glycoprotein substrates were excluded. They analysed 38 datasets for 14 drugs tested in healthy young males and females. They found a difference in the overall mean ratios of female to male weight-normalized clearance of the drugs (parenteral drugs: 1.26 ± 0.07; oral drugs: 1.17 ± 0.07), i.e., women cleared the drugs faster than men. In conjunction with this finding, they also looked at absolute bioavailability of the oral drugs and identified no difference in this parameter between males and females. The authors concluded that gender had a small and statistically significant influence on CYP3A metabolism, although they felt that it was probably not clinically important. This study indicates that additional parameters may need to be characterized to determine sex differences in drug metabolism.

In 2010, Hu and Zhao published a meta-analysis on sex-dependent differences in midazolam disposition for both intravenous and oral exposures.[26] The studies showed that women had higher clearance rates than men, men had higher AUCs, and the sex differences were more pronounced for intravenous midazolam. There was no difference in oral bioavailability between the sexes. They concluded that women exhibited significantly greater hepatic CYP3A activity than men.

Chetty and colleagues attempted to simulate how different substrates are handled by the CYP3A enzymes.[27] The aim was to identify how a human study might need to be designed. They noted that the lack of consensus in the literature regarding male vs. female metabolism may be explained by underpowered and inconsistent study design. Focus was on the CYP3A isoforms because they are common, responsible for a broad range of drugs, are more highly expressed, and have greater activity and reproducibility in women. Five drugs that are CYP3A substrates not transported by P-glycoprotein and have published clinical data

were selected for simulation: midazolam (oral), nifedipine, triazolam, alprazolam and zolpidem. The patient population was set to be Northern European Caucasian males and females with an age range of 19 to 45 years and body composition based on the Simcyp v8.2 population library.[i] The simulations were then set to estimate systemic clearance of the drugs and to determine the required number of subjects to identify a difference between males and females in the metabolism of these drugs. The results indicated that the following numbers of subjects per study were needed for an 80% probability of identifying a higher weight-adjusted clearance in females than males: alprazolam: 105, nifedipine: 120, triazolam: 150, oral midazolam: 300.[27] Most pharmacokinetic studies have fewer than 100 subjects and thus have insufficient power to demonstrate a difference in metabolism between males and females. We now wonder how to interpret earlier pharmacokinetic studies, where this sex-based difference was not addressed or the subject numbers were not large enough to indicate a difference.

Elimination

We know that there are differences between men and women with respect to renal drug clearance as a result of differences in blood flow, filtration and secretion. Digoxin is a drug that has been used for well over 100 years, is not completely cleared renally, and is an interesting drug in terms of elimination and toxicity. In a study of digoxin-related toxicity, Aarnoudse and colleagues reviewed all hospital admissions in The Netherlands from 2001 to 2004 and selected those related to digoxin toxicity.[28] They then correlated the incidence of digoxin toxicity leading to hospitalization, by patient age, against the number of prescriptions dispensed. The analysis found that women had a 1.4-fold higher risk for intoxication than men. This risk was relatively steady over the various age groups for women, but increased for men as they aged.

In 2002, Rathore and colleagues published a *post hoc* analysis on the differences between men and women in the effects of digoxin.[29] The analysis was based on a placebo controlled study of the effect of digoxin on morbidity and mortality in the treatment of heart failure.[30] The original study authors found that women with heart failure experienced a higher risk of death due to any cause (absolute difference of 5.8% over men) if they had been treated with digoxin.[30] This risk was not evident in men. There were not dramatic differences between men and women in study drug doses, doses per body mass index, and serum concentrations. Therefore, questions arise as to whether it is pharmacodynamic differences or other factors that are putting women with heart failure at risk of mortality when treated with digoxin.

Yukawa and colleagues recently published a study on factors affecting digoxin clearance after oral dosing in elderly patients.[31] Their model showed that female sex was among a number of variables influencing digoxin clearance.

SUMMARY

In closing, we'll look at type 2 diabetes, a disease that poses a significant global public health challenge.[32-34] It is estimated that about 7.7% of the world's adult population will have diabetes in the year 2030.[35] Diabetes is a risk factor for cardiovascular disease and diabetic women seem to be at a slightly higher risk of dying from cardiovascular disease (OR = 2.9) than men (OR = 2.3).[36]

Our group has access to the Cerner Health Facts® data warehouse, which is a database of electronic medical record data at the detail, time-stamped, level, allowing longitudinal tracking of patients and the sequence of their care. Health Facts® now contains 156 million electronic medical records for over 35 million patients from 500 U.S. healthcare institutions followed for up to 12 years. We currently have an experimental database of about 600,000 patients with type 2 diabetes, which can allow us to look into actual circumstances surrounding the management and outcomes of these patients, including the safety

[i] "Simcyp Limited provides platforms for the modelling and simulation of pharmacokinetics and pharmacodynamics in virtual human populations…" https://apps.simcyp.com/About.aspx (May 31, 2013)

and effectiveness of antidiabetic agents and how they are being used.

Diabetes predisposes to the development of cardiovascular disease. Some antidiabetic medications may also be implicated in causing cardiovascular toxicity. We therefore reviewed patient data from the Cerner Health Facts® data warehouse to determine crude cardiovascular adverse event rates. The percentages of patients experiencing heart failure, myocardial infarction, or heart failure plus myocardial infarction, were graphed against oral antidiabetic agents: metformin, pioglitazone, rosiglitazone, insulin and sulfonylureas . Crudely, the adverse event rates of males and females appeared comparable. However, for some drugs the risk of adverse events may accrue over years of exposure. We then graphed the odds ratios for pioglitazone, rosiglitazone, insulin and sulfonylureas compared to metformin for acute myocardial infarction (AMI) as a function of treatment exposure (from 1 to 9 years). The graphs showed differences over time, with some treatments seeming to lower the risk of AMI and others increasing it. Yet we do not know whether the changes are related to the medication, to the nature of the disease, or to other factors. In women there was an increasing odds ratio for AMI over time for pioglitazone vs. metformin. This was not replicated in men.

These early, and not definitive, experiments are designed to help us tease out disease- and treatment-related differences between the sexes. They begin to show us that greater attention needs to be paid to understanding the effectiveness and safety of the drugs we use in both men and women.

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