Potential Drug Dosing Variability in Women

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Objectives

- Understand the pharmacokinetic variability found in the elderly, female patient.
- Discuss specific changes found in each pharmacokinetic phase (absorption, distribution, metabolism, and elimination)

Dose → Response

Influencing Factors (response):

- Dose (bioavailability)
- Age
- Weight (Obesity)
- Sensitivity
- Renal/Hepatic Function
- Genetics
- Responder/Nonresponder
- Race
- Gender
- Interactions with other meds/herbals
- Smoking and alcohol use
- Diet

Pharmacokinetic Principals (dictates amount available)

- Absorption
- Distribution
- Metabolism
- Elimination

Absorption (Bioavailability)

- Are gender differences clinically significant?
- Gastric pH higher in women
  - Some medications require acid to be absorbed
  - Loss of gastric acid production continues as you age
- Bowel transit time are usually longer
- Inactive ingredients may affect absorption
  - Polyethylene glycol enhances bioavailability of ranitidine (Zantac) in men by up to 63%
    - Decreased in women up to 24%

Distribution

- Women have a higher percentage of adipose mass vs. men (25% vs 16%)
  - Difference less as we age
- Accumulation of lipophilic drugs in adipose tissue such as benzodiazepines (e.g., Valium, amitriptyline)
  - Prolonged half-life
  - Tissue accumulation
  - Exposure-related adverse effects

Distribution

- Women have a lower plasma volume than men
  - Plasma volume continues to decline as you age
  - May affect drugs that are water soluble
  - Potential for increased blood concentrations and increased activity: ex: ethanol, acetaminophen and digoxin
- Lower organ blood-flow rate
  - Continues to decline as you age
  - Decreased cardiac output

Metabolism

CYP Enzyme	Gender differences in activity	Examples
CYP1A2	Women < men	Clozapine (Clozaril) Olanzapine (Zyprexa)
CYP2D6	Women < men	Dextromethorphan Metoprolol (Lopressor)
CYP3A	Women > men	Midazolam (Versed), Nifedipine (Procardia), Triazolam (Halcion)
CYP2C9	Women = men	Fluvastatin
CYP2C19	Women = men	Mephenytoin

< (decreased metabolism, greater exposure)
> (greater metabolism, less exposure)
= (similar metabolism and exposure)

Metabolism

- Lower rate of blood flow to the liver
  - Decreased delivery of medications to the liver
- Women take more prescription medications and OTC/herbal products than men
  - Potential for greater exposure due to a higher frequency of drug-drug-interactions

Renal Excretion

- Renal clearance generally higher in men
  - Body weight differences
  - GFR directly proportional to lean body weight
- As we age:
  - Beginning at age 40, ~10% reduction in GFR & renal plasma flow per decade
  - By age 70 a person may have a decrease of up to 70 %, even in the absence of kidney disease
    - decrease in muscle mass due to normal aging
    - decrease production of creatinine.

Calculating CrCl

1. Measure serum creatinine
   - Plasma concentration
   - 24 hour urine collection
2. Patient's age (years)
3. Patient's weight (kg)

$$CrL = \frac{(140 - age)^* wt}{72 * SrCr}$$

Multiply by 0.8 for women

Normal Results of the Aging Process

- Alterations in body composition
  - a increase in body fat
  - b decrease in fat free mass
  - c decrease in total body water
  - d decrease in serum albumin concentration
  - e decrease in visceral blood flow
  - f increase in bone loss

Gender Differences - Pharmcodynamics

- Lengthening of the QT interval
  - Women at greater risk to develop torsade de pointes from drugs that prolong cardiac repolarization
  - Effect of sex hormones on activity of potassium channels
    - Progesterone may have a protective effect
  - Greatest QTc response found during the menstrual and ovulation phases of the cycle.
  - Monitor and reduce risk
    - Serum electrolyte levels (low potassium and or magnesium)
    - Ischemia
    - Concurrent use of other drugs that prolong the QTc interval

Medication Examples

- Statin induced myopathy
  - Women
  - Frail individuals
  - Low body mass index
  - Hypothyroidism
  - Poly-pharmacy
  - Alcohol abuse
  - Vitamin D deficiency
    - Use CYP enzymes for vitamin D hydroxylation
    - Increase exposure to statin

Medication Examples

- 2012 study revealed a 35% higher risk of hip fracture in women regularly using PPIs for at lest 2 years
  - Decreased absorption of calcium
  - Association stronger in current and former smokers

Medication Examples

- Selective Serotonin Reuptake Inhibitors
  - Beers drugs due risk of falls and hyponatremia due to SIADH
  - Risk factors
    - Older age
    - Female sex
    - Low body weight
    - Use of diuretics
    - Baseline hyponatremia
  - Monitor sodium levels
    - Especially if above risk factors

Medication Examples

- Amlodipine (Norvasc)
  - Possible increase risk of adverse events in women on higher doses
  - Bioavailability higher in women
  - More often in women of lower body weight

Adverse Event	Male (%) (N=1218)	Female (%) (N=512)	Male (%) (N=914)	Female (%) N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

Medication Examples

- Zolpidem (Ambien)
  - Beers medication
  - Metabolized in the liver
    - Increased exposure in patients with liver impairment
    - FDA product labeling change: no more than 5 mg in the elderly
  - Rate of absorption higher in women vs men
    - 45% higher for immediate release tablet
    - 50-75% higher for sustained release tablet
  - January 2013 FDA Safety Alert
    - Initial dose immediate-release: 5 mg for women and either 5 mg or 10 mg for men.
    - Initial dose of zolpidem extended-release is 6.25 mg for women and either 6.25 or 12.5 mg for men.
    - Lower doses not effective, increase to 10 mg for immediate-release products and 12.5 mg for extended-release
      - Increase risk of next-day impairment of driving and other activities that require full alertness.

Overall Goal: Avoid Adverse Events

- Beers List
  - Standard for inappropriate medications
  - At least 23% of older adults take ≥ 1 medications on Beers List
  - Linked to poor health outcomes
    - Higher risk of hospitalization or ED evaluation
    - http://onlinelibrary.wiley.com/doi/10.1111/jgs.13702/pdf
    - There's an app for it!

What can we do: Putting it all together

1. Accurate and comprehensive medication assessment
2. Use of strategies to optimize medication use while minimizing risk of adverse drug events
3. Collaboration with all members of interdisciplinary team
4. Staff and family education

Questions