Sex, gender and drugs
A webbased knowledge databank

Karin Schenck-Gustafsson,
Prof., MD, PhD, FESC, MD h.c.
Founder and chair, Centre for Gender Medicine, KI

Mia von Euler MD, PhD, Assoc. Prof.
Linnea Karlsson, PhD student, Pharmacist
Desirée Loikas, PhD student, Pharmacist
Björn Wettermark, Pharmacist, Assoc.Prof.
Seher Korkmatz, MD, PhD

This project the European Gender Medicine Network (EUGenMed) has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement No 602050.
Sex and gender and drugs

- Women and men are different
  - body size, organ function, hormones, enzymes (= sex)
  - behaviors, expectations (= gender)

- Descriptive reports of gender differences in drug use – some without medical grounds

- Sex can affect pharmacokinetics, pharmacodynamics and side effects of drugs

- Sex or gender analysis are often lacking in drug evaluation studies

Karin Schenck
Men and women handle drugs differently

Absorption
Distribution
Metabolism
Elimination
Pharmacodynamics


Karin Schenck
Men and women are different

Table I. Anatomical differences between men and women

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference adult male</th>
<th>Reference adult female</th>
<th>Reference pregnant female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodyweight (kg)(^a)</td>
<td>78</td>
<td>68</td>
<td>72.5</td>
</tr>
<tr>
<td>Height (cm)(^a)</td>
<td>176</td>
<td>162</td>
<td>162</td>
</tr>
<tr>
<td>Body surface area (cm(^2))</td>
<td>18 000</td>
<td>16 000</td>
<td>16 500</td>
</tr>
<tr>
<td>Total body water (L)</td>
<td>42.0</td>
<td>29.0</td>
<td>33.0</td>
</tr>
<tr>
<td>Extracellular water (L)</td>
<td>18.2</td>
<td>11.6</td>
<td>15.0</td>
</tr>
<tr>
<td>Intracellular water (L)</td>
<td>23.8</td>
<td>17.4</td>
<td>18.8</td>
</tr>
</tbody>
</table>

\(^a\) Data from Ogden et al.\(^4\) With an increasing percentage of fat, these numbers will be skewed to the right; this would be an important indicator for (very) large intersubject variability in pharmacokinetics and other parameters.

### Adverse drug reactions more common in women

#### Table II. Suggested reasons for sex differences in adverse event reporting

<table>
<thead>
<tr>
<th>Reason for sex difference</th>
<th>Pharmacological reason</th>
<th>Pharmacological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women are more frequently overdosed than men</td>
<td>Pharmacokinetics</td>
<td>The volume of distribution (V_d) is often larger</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The free fraction is larger (significant for low-elimination-rate drugs monitored by therapeutic drug monitoring)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clearance can be increased or decreased depending on the pathway of elimination</td>
</tr>
<tr>
<td>Women are more sensitive than men</td>
<td>Pharmacodynamics</td>
<td>Differences in receptor numbers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Differences in receptor binding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Differences in the signal transduction pathway following receptor binding</td>
</tr>
<tr>
<td>Women take a greater amount of medications than men</td>
<td>Drug interactions</td>
<td>Differences in pharmacokinetics (see above)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Differences in pharmacodynamics (see above)</td>
</tr>
</tbody>
</table>
First placebo controlled clinical heart-failure study with digitalis:
No difference in survival between female and male patients

But a post-hoc analysis showed:
Women had increased mortality compared with men.
A drug for men only?
Dangerous side effect -70% in women

Torsade de pointe –ventricular tachycardia -dangerous arrhythmia

induced by ex: antiarrythmic drugs,

antiallergic drugs, antidepressant drugs
Other Examples, important sex differences

ACE-inhibitors for heart failure and hypertension – more cough in women

Calcium-channel blockers for hypertension - more peripheral edema in women

Clopidogrel - women bleed more

Zolpidem for insomnia - half the dose for women

Lamotrigine for epilepsy and bipolar disease - increased dose in pregnancy

Schenck

This project the European Gender Medicine Network (EUGenMed) has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement No 602050.
Withdrawn medications with serious adverse effects mostly in women

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of Drug</th>
<th>Patient Population</th>
<th>Primary Health Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pondimin</strong></td>
<td>Appetite suppressant</td>
<td>Women</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td><strong>Redux</strong></td>
<td>Appetite suppressant</td>
<td>Women</td>
<td>Valvular heart disease</td>
</tr>
<tr>
<td><strong>Rezulin</strong></td>
<td>Diabetic</td>
<td>Women</td>
<td>Liver failure</td>
</tr>
<tr>
<td><strong>Lotronex</strong></td>
<td>Gastrointestinal</td>
<td>Women</td>
<td>Ischemic colitis</td>
</tr>
<tr>
<td>Seldane(^a)</td>
<td>Antihistamine</td>
<td>Women and Men</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td><strong>Posicor</strong></td>
<td>Cardiovascular</td>
<td>Women and Men</td>
<td>Lowered heart rate in elderly women and adverse interactions with 26 other drugs</td>
</tr>
<tr>
<td><strong>Hismanal</strong></td>
<td>Antihistamine</td>
<td>Women and Men</td>
<td>Torsades de Pointes</td>
</tr>
<tr>
<td>Propulsid(^b)</td>
<td>Gastrointestinal</td>
<td>Women and Men</td>
<td>Torsades de Pointes</td>
</tr>
</tbody>
</table>

Source: GAO analysis in GAO-01-286R Drugs Withdrawn From Market 2997-2001
Drug utilization in Sweden, women take more

Drug utilization data from Swedish Board of Health and Welfare:
59% of all Swedish men and 75% of all Swedish women take out at least one doctors prescribed drug per year (2010)

- Swedish Board of Health and Welfare, Drug registry
- Loikas D et al, BMJ Open 2013
Drug utilization in Sweden (10 million inhabitants) all dispensed drugs at pharmacies (men, women, age)
"Unique website will help with drug prescription Gender at Janus"  www.janusinfo.se/genus
Soon everything in English
Sex, gender and drugs - How?

- Standard litterature
- Structured Pub Med search and other databases
- Short conclusion and recommendation
- More extensive information on sex differences in:
  - Pharmacokinetics
  - Dosing
  - Effect
  - Adverse effects
  - Additional information
  - Swedish dispensation data
  - References

- Evidence grading
- Discussed in panel and sometimes with FDA and Swedish MPA
Köns- och genusspekte vid läkemedelsförskrivning

Warfarin

Bedömning
Warfarin reducerar risken för tromboembolism lika effektivt hos både kvinnor och män. Några studier framhåver en potentiellt högre nyttja hos kvinnor [1].

Kvinnor som tar warfarin har en högre risk för stroke jämfört med män som tar warfarin [2].

Kvinnor kan behöva en lägre dos warfarin än män för att bibehålla ett terapeutiskt INR-värde [3].

Bledningsrisken av warfarin är likartad hos både kvinnor och män [1].

Förskrivningsstatistik
Läkemedelsuttag av warfarin är vanligare bland män än kvinnor i Sverige i åldern 35 år och uppst. Under 2011 användes warfarin i genomsnitt av 22,5 manliga patienter/1000 invånare i åldernsgrupp 0-85 år, medan motsvarande siffror för kvinnor var 15,6 patienter/1000 invånare [4].

Background
Studies shows that warfarin is equally effective in reducing the risk of thromboembolism in both men and women [1]. A comparative study observed that women were at higher risk for thromboembolism than men at both younger and older ages. Adjusted RR for women versus men was 1.6 (95% CI, 1.0 to 2.5) for those <75 years of age and 1.8 (95% CI, 1.4 to 2.3) for those ≥75 years of age. Warfarin therapy was associated with a significant reduction in the rate of thromboembolism with an adjusted RR of 0.4 (95% CI, 0.3 to 0.5) in women and 0.6 (95% CI, 0.5 to 0.8) in men. In multivariable models including patients both on and off warfarin therapy, the reduction in rates of thromboembolism with warfarin was larger in women than in men [5].

A multicenter study in Canada showed that women on warfarin were 3.35 times more likely to experience a major bleed, compared with men [6].

datum: 2012-11-23

Referenser

2. McKenna R, Cole ER, Vasan U. Is warfarin sodium contraindicated in Published

### Computer Based Prescription Support

#### "Genderbutton"

Schenck
Först 100 drugs: 25 % change in recommendations

Often because of missing info!

Schenck

This project the European Gender Medicine Network (EUGenMed) has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement No 602050.
What can we gain

Fewer drug complications

Right doses on right indications

Save money

Safer, more effective care

Better understanding of sex and gender aspects

Schenck

This project the European Gender Medicine Network (EUGenMed) has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement No 602050.