Gender Differences in the Effects of Alcohol and the Role of the Menstrual Cycle

M. Mumenthaler, J. Taylor, J. Yesavage

California Association of Toxicologists Meeting
August 2, 2003
Issues in Flight Safety

- Alcohol effects 8 hr after drinking
- Gender differences in drug effects due to differences in drug metabolism?
- Hormone effects on post-drink performance?
Today's Topics

1. Discuss general alcohol issues
2. Introduce flight simulator testing methods
3. Discuss results of our studies on gender differences in alcohol effects
4. Discuss results of our studies on the interaction of menstrual cycle and alcohol
Alcohol is a Unique Substance

- Extremely weak; low pharmacologic potency
- Consumed in extremely high doses (30 x Aspirin)

**Alcohol elimination** - zero order; linear; concentration-independent

99% of all other drugs - first order; exponential; concentration-dependent
Alcohol Concentration in Percent

- Beer: 5%
- Wine: 10%
- Port wine: 20%
- Liqueurs: 30%
- Gin, Vodka: 40%
- Whiskey: 50%
- Rum: 60%
“Standard Drink”

NIAAA Definition:

- = 12 oz = 3.0 dl beer
- = 5 oz = 1.5 dl wine
- = 1.5 oz = 0.5 dl liqueur

\{ 15 g Alcohol \}
Factors Influencing BAC

- **Weight** of the person
  - The lighter, the higher the BAC
- **Food** in stomach
  - The less, the higher the BAC
- **Concentration** of the drink
  - Highest BAC with 15-30% solution
- **Time** between drinks
  - The shorter, the higher the BAC
- Genetics; individual variation
- Gender?...
Alcohol is Common in Aviation

**General Aviation**
Alcohol is involved in 10-30% of all fatal crashes due to pilot errors.

**Commercial Aviation**
Cases where pilots had illegal alcohol concentrations upon terminating their missions.

**General and Commercial Aviation in USA**
> 10’000 pilots had their driver’s licenses withdrawn at least once due to alcohol
Flight Scoring

Summary score

Take-off
- Course
- Speed
  - Time
  - Direction
  - Distance

Traffic Avoidance
- Heading
- Radio
- Squawk

Communications
- Oil Pressure
- Carburetor Ice

Emergencies
- Course
- Altitude
- Aileron

Approach
- Vertical Speed
- Heading
- Distance to TD
- Distance to Cent.

Landing
- Summary score
- Flight Scoring
Results: How Long are Pilots Impaired?

- Impairment of flight performance up to 14 hr after drinking
Eight hr After Drinking

- No more detectable alcohol in the blood
- Impaired psychomotor precision
- Impaired execution of ATC commands
- Pilots underestimate impairment

Alcohol can impair flight performance up to at least 12 hr after drinking – even at 0% BAC
## Gender Differences: Elimination

<table>
<thead>
<tr>
<th>Study</th>
<th>N Men</th>
<th>N Women</th>
<th>Dose</th>
<th>$\beta^{60}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al. 1996</td>
<td>11</td>
<td>12</td>
<td>0.77 m; 0.67 w</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Ammon et al. 1996</td>
<td>6</td>
<td>6</td>
<td>0.3</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Thomasson 1995a</td>
<td>45</td>
<td>45</td>
<td>0.6 m; 0.5 w</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Thomasson 1995b</td>
<td>56</td>
<td>56</td>
<td>0.54</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Smith et al. 1993</td>
<td>11</td>
<td>9</td>
<td>0.8</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Frezza et al. 1990</td>
<td>14</td>
<td>17</td>
<td>0.3</td>
<td>M~W</td>
</tr>
<tr>
<td>Mishra et al. 1989</td>
<td>9</td>
<td>9</td>
<td>0.6</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Sutker et al. 1987</td>
<td>10</td>
<td>8</td>
<td>0.50; 0.76</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Cole-Harding 1987</td>
<td>75</td>
<td>63</td>
<td>0.8</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Holtzman et al. 1985</td>
<td>7</td>
<td>5</td>
<td>45g/day</td>
<td>M&lt;W*</td>
</tr>
<tr>
<td>Martin et al. 1985</td>
<td>194</td>
<td>208</td>
<td>0.75</td>
<td>M~W</td>
</tr>
<tr>
<td>Arthur 1984</td>
<td>10</td>
<td>10</td>
<td>0.5</td>
<td>M~W</td>
</tr>
<tr>
<td>Jones &amp; Jones 1976</td>
<td>10</td>
<td>20</td>
<td>0.5</td>
<td>M~W</td>
</tr>
</tbody>
</table>
Gender Differences: BAC-Time Curve


Mumenthaler et al. Alcohol Research and Health 1999; 23(1):55-64.
Why Gender Differences in Metabolism?

- More body fat, less water in women
- Lower first-pass metabolism in women
  - In GIT?
  - In liver?
- Larger liver volume per body water in women
- Higher peak BAC activates additional enzyme system in women?
- Testosterone inhibits elimination in men
- Influence of female sex hormones?...
Prior Studies: Gender Cognitive Differences

Results of specific (computer) tests:

<table>
<thead>
<tr>
<th>Worse impairment in women</th>
<th>No gender difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cognitive performance</td>
<td>• Psychomotor</td>
</tr>
<tr>
<td>• Short term memory</td>
<td>performance</td>
</tr>
<tr>
<td>• Divided attention</td>
<td>• Eye-hand</td>
</tr>
<tr>
<td></td>
<td>coordination</td>
</tr>
</tbody>
</table>

* Differences larger at higher BAC
Gender Differences in Flight Performance?

Baseline

Acute Intoxication

8-h Carryover

Men

Women
Conclusions:

- Women reach significantly higher BAC than men
- Women eliminate alcohol significantly faster than men
- These pharmacologic differences do not seem to significantly influence post-drink flight performance
Study: Effects of MC on Alcohol PK

- Does the menstrual cycle influence Alcohol pharmacokinetics?
- Alcohol-induced flight performance impairment?
Subjects

- 26 licensed female pilots
- 21-40 years of age
- Moderate drinkers (M = 4.1 drinks/week)
- Not taking oral contraceptives
- Regular menstrual cycle
8 h flight simulator training (6 Days)

2 test days:

- Menstrual vs. Luteal

Within-subjects design
Phases of the Menstrual Cycle

Day of the Menstrual Cycle

01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

- Ovulatory
- Luteal/Postovulatory
- Follicular/Preovulatory
- Premenstrual
- Menstrual
Hormone Levels During the Menstrual Cycle

The diagram illustrates the changes in hormone levels during the menstrual cycle. Key stages include:

- **Menstruation**: The period when menstrual flow occurs.
- **Ovulation**: The release of an egg from the ovary.
- **Luteal Test Day**: A specific day used for testing during the luteal phase.

The graph shows the hormone levels over the menstrual cycle, with peaks indicating changes in hormone activity.
Mean Luteal Increase in Hormone Levels

- Estradiol Spiegel in pg/mL
- Progesterone Spiegel in ng/mL

Estradiol Spiegel in pg/mL:
- Mean Luteal Increase

Progesterone Spiegel in ng/mL:
- L (Light Yellow)
- M (Red)
## Typical Test Day

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0700</td>
<td>Standard Breakfast</td>
<td></td>
</tr>
<tr>
<td>0730</td>
<td>Flight 1: Baseline</td>
<td>3 test flights (75 min each )</td>
</tr>
<tr>
<td>0900</td>
<td>Alcohol Ingestion</td>
<td>&gt; 20 BrAC</td>
</tr>
<tr>
<td>1000</td>
<td>Flight 2: Acute</td>
<td></td>
</tr>
<tr>
<td>1030</td>
<td>Maintenance Drink</td>
<td>Total of 13 h</td>
</tr>
<tr>
<td>1115</td>
<td>Rest, Lunch, Rest</td>
<td></td>
</tr>
<tr>
<td>1830</td>
<td>Flight 3: 8-h Carryover</td>
<td></td>
</tr>
</tbody>
</table>
Results: BAC-time Curves

One-compartment Open Model

GI Tract $q_a$ $\rightarrow$ $k_a$ $\rightarrow$ Lean Body Mass $C$

Input $\rightarrow$ $k_e$

$V_{max}, K_m$
Two-compartment Open Model

GI Tract $q_a$

Input

$V_{max}, K_m$

Lean Body Mass $C$

$ke$

Tissue
Curve Fit to Mean BrAC-t Data

BrAC (g/liter) vs. Time (hr)
Retest of Five Pilots

![Graph showing BAC (g/L) over time for Original Test and Retest with Luteal and Menstrual Mean curves.](image)
Results: Pharmacokinetics

No significant influence of menstrual cycle on

- peak BAC
- Absorption ($k_a$)
- Elimination ($\beta_{60}$, $b_{60}$, $R$, $V_{max}$, $K_m$)
- AUC

No correlation between $E_2$, $P$ and Pharmacokinetics

Results: Overall Flight Performance

Baseline

Acute Intoxication

8-h Carryover

Menstrual Phase

Luteal Phase
Elimination Rate – Flight Performance

Alcohol Elimination (g/h)

Recovery at Carryover (z-scores)

○ Luteal

□ Menstrual
Alcohol and MC: Conclusions

Pharmacokinetics

- Earlier speculations not confirmed
- MC ≠ explanation for gender differences
- Unlikely that MC influences alcohol metabolism

Performance

- MC did not affect flight performance
- Variations in MC have little biological significance in pilot’s workplace
Looking for

PILOTS WHO SMOKE

for NEW research study at Stanford University

EARN $750.00 + free sim. time!

You will be flying our Frasca 141 simulator
(time commitment approx. 40 hr).
We will study the Effects of Nicotine Withdrawal on Aviator Performance.

To participate you must:
• be a licensed pilot with a current FAA medical certificate
• be 20-60 years of age
• be a smoker who smokes approx. 15 cigarettes/day or more

For information, please contact Lisa Wilson:
(650) 493-5000 x 66040 or lisa.wilson@stanford.edu