Drugs (and Biologics) in Semen Symposium

Introduction

Bruce Beyer
On behalf of HESI DART Technical Committee

With acknowledgements to Tony Scialli for several slides and Connie Chen (HESI) for background material

MARTA 29 Oct 2014
Background information

- Potential for male-mediated developmental effects not well characterized
- Seminal transfer of drugs resulting in exposure to conceptus by:
  - Transfer into oocyte following adsorption onto sperm
  - Systemic absorption from vagina → placental transfer to embryo-fetus OR local counter-current transfer to uterine artery
  - Penetration through cervical mucous barrier → direct entry into intrauterine environment
Animal models demonstrated some small molecules enter semen

- Some antimicrobials concentrate in semen at >10-fold in seminal concentration vs. plasma
  - Theoretical possibility that exposure of female partner and conceptus to drugs in semen could be significant
  - Small volume (1-5 mL) of transferred semen limits systemic exposure
  - Unlikely for such negligible exposure to reach physiologic levels

- No published data assessing potential seminal transfer of large molecule pharmaceuticals (e.g., mAbs)
Review Article

The Transport of Chemicals in Semen

Leah Klemmt\textsuperscript{1} and Anthony R. Scialli\textsuperscript{2*}

\textsuperscript{1}College of William and Mary, Williamsburg, Virginia
\textsuperscript{2}Sciences International, Inc., Alexandria, Virginia

Three mechanisms have been proposed for exposure of the conceptus to chemicals in semen: access of chemicals to the maternal circulation after absorption from the vagina, direct chemical exposure of the conceptus following transport from the vagina to the uterine cavity, and delivery to the egg and subsequent conceptus of chemical bound to the sperm cell. We review published data for each of these three mechanisms. Human seminal fluid chemical concentrations are typically similar to or lower than blood concentrations, although some antimicrobial agents achieve higher concentrations in semen than in blood. Vaginal absorption of medications has been shown to occur, although the vehicles in which these medications are delivered to the vagina may maintain contact with the vaginal epithelium to a greater extent than does semen. Assuming total absorption of a seminal dose of a chemical with a high semen:blood concentration ratio, distribution within the recipient woman would result in a blood concentration at least three orders of magnitude lower than that in the man. Direct delivery of seminal chemicals into the uterine cavity of humans has not been shown to occur, although it may occur in species such as the rat in which seminal fluid has access to the uterine cavity. Chemicals in or on human sperm cells have been demonstrated with respect to tetracycline and cocaine in vitro and aluminum, lead, and cadmium in vivo. The in vitro cocaine study offers sufficiently quantitative data with which to predict that oocyte concentrations would be five orders of magnitude lower than blood concentrations associated with cocaine abuse, assuming a maximally cocaine-bound sperm were capable of fertilizing. Thus, even using liberal assumptions about transmission of chemicals in semen or sperm, predicted exposure levels of a pregnant woman or of
<table>
<thead>
<tr>
<th>Drug</th>
<th>Blood</th>
<th>Semen</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin</td>
<td>2.87</td>
<td>26.76</td>
<td>9.33</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.2-0.9</td>
<td>2-7</td>
<td>7-9</td>
</tr>
<tr>
<td>Enoxacin</td>
<td>0.9</td>
<td>5.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>1.26</td>
<td>5-7</td>
<td>~4</td>
</tr>
<tr>
<td>Cefalothin</td>
<td>2.71</td>
<td>9.64</td>
<td>3.55</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2.99</td>
<td>4.08</td>
<td>1.36</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>17.94</td>
<td>10.89</td>
<td>0.6</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1.2</td>
<td>0.55</td>
<td>0.45</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>2.28</td>
<td>9.95</td>
<td>0.24-1.86</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>13.8</td>
<td>2.31</td>
<td>0.17</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2-9</td>
<td>0.2-1</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>4.58</td>
<td>0.66</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Immunoglobulins in semen

- Prostatic source
  - Prostate contributes ~25-30% of seminal fluid components

- Transudation from serum

- Semen IgG 1% of serum IgG
  - IgG\textsubscript{1} 51%
  - IgG\textsubscript{2} 43%
  - IgG\textsubscript{3} 1%
  - IgG\textsubscript{4} 5%

Regulatory concerns 1/2

- Regulatory authorities concerned about potential risk of embryo-fetal harm through exposure of pregnant females to pharmaceuticals in seminal fluid
- UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued guidance for acceptable contraceptive and barrier protection requirements for clinical trial protocols to limit seminal transfer of drugs to untreated sexual partners and their progeny
- But no global guidance or implementation of barrier protection for men in clinical trials
- Most companies do not routinely assess semen drug concentrations
Regulatory concerns 2/2

- **MHRA (UK) guidance:**
  Contraceptive requirements for male subjects with partners of childbearing potential should be included in the protocol where needed. These requirements should also extend to a suitable period after the last dose of study medication (e.g., a whole spermatogenic cycle or five half-lives) and should be based upon the availability and results of reproductive toxicity data.

- **How do results of animal embryo-fetal studies matter?**
- **How does the concentration in semen matter?**
Volume of distribution

• Depends on
  – Lipid solubility
  – Plasma protein binding
  – Tissue binding

• 70 kg woman
  – Blood volume 5.5 L
  – Extracellular fluid 12 L
  – Total body water 42 L
  – 20-25% ↑ in pregnancy
Methicillin as an example

- Male blood concentration 2.87 mg/L
- Semen concentration 27 mg/L
- Semen (volume 5 mL) contains 0.135 mg
- Assume 100% vaginal absorption
- Assume distribution only in blood (6.6 L)
- Maternal concentration 0.02 mg/L (<1% of male)
Are there other mechanisms for transport to the embryo?
Countercurrent transfer

Vaginal artery and vein

a, b, c + d)

Vagina
Countercurrent transfer of progesterone

Vaginal progesterone in menopausal women

- Endometrial effects greater than predicted by systemic exposure
- Higher ratio of endometrial:serum progesterone concentration than IM route
- Higher uterine progesterone concentration than in radial artery

Other examples

- Estradiol
- Technetium-99m
Transcervical transport

Barrier to:
- Sperm
- Microorganisms
- Chemicals?????
Cervical mucus

- Produced by endocervical crypt cells
- Glycoproteins (mw $10^7$) exclude large molecules (steric hindrance)
- Negative charges trap cations

Reviewed by Becher et al., Acta Obstet Gynecol 2009;88:502
Attachment to sperm

- 3600 cocaine binding sites/sperm cell
- Motility not affected
- Volume of human oocyte = 3.59 nL
- Fully bound sperm would result in $6 \times 10^{-12}$ M cocaine (5 x $10^{-7}$ mg/L)
- Recreational blood cocaine concentrations ~1 mg/L.
Other sperm binders

- Tetracycline
- Thalidomide
- Cadmium
- Lead
- Aluminum
HESI DART Drugs/ Biologics in Semen Project 1/3

- HESI DART Technical Committee formed consortium to assess potential exposure and toxicity risk to female partner and developing conceptus from seminal drug transfer
- Series of experiments performed to provide data for understanding exposures and potential for male-mediated developmental toxicity due to seminal drug transfer of both small and large molecules
- Data intended to inform companies and regulators of extent of exposure and toxicity risk, and need for use of contraception/barrier protection for partners of treated males in clinical trials
HESI DART Drugs/ Biologics in Semen Project 2/3

• Experimental studies:
  – NHP intravaginally dosed with metronidazole
    • Maternal/fetal exposure
    • Determine if traditional fetal exposure modeling conservative enough to predict potential fetal risk
  – NHP intravaginally dosed with IgG2 mAb biweekly during gestation
    • Maternal/fetal exposure
  – Rabbits orally and intravaginally dosed with thalidomide
    • Compare route-specific differences in maternal/embryonic exposure and developmental toxicity
HESI DART Drugs/ Biologics in Semen Project 3/3

• Experimental studies (continued):
  – Male and PG female rabbits dosed with IgG4 mAb
    • Assess seminal excretion
    • Vaginal vs. intravenous absorption
    • Placental transfer
  – PG and non-PG rats and mice intravaginally dosed with trypan blue dye
    • Assess potential for direct fetal exposure via transcervical passage
  – Optical imaging of β-actin luc transgenic mouse intravaginally dosed with D-luciferin reporter substrate
    • Maternal / embryo-fetal exposures assessed
    • Influence of estrous cycle stage on D-luciferin distribution in female reproductive tract also assessed

• Results published as part of ETS proceedings:
  – Reproductive Toxicology 48:113-147 (2014)
Backup Slides

(Courtesy of Tony Scialli)
Components of semen

- Seminal vesicles 65-75%
- Prostate 25-30%
- Testis 2-5%
- Cowper's gland <1%
## Vaginal absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Bromocriptine</td>
<td>Vaginal absorption results in decreased prolactin</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Vaginal wash during labor → detectable blood levels</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>4% of cream and 20% of the ovule absorbed</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>2-10% estimated absorption</td>
</tr>
<tr>
<td>Estrone or</td>
<td>Absorbed in menopausal women; peaks comparable to follicular phase</td>
</tr>
<tr>
<td>estradiol</td>
<td>concentrations</td>
</tr>
<tr>
<td>Hexachlorophene</td>
<td>Detectable in maternal and cord blood</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Serum concentrations up to 1.156 mg/L (10% of oral trough)</td>
</tr>
<tr>
<td>Miconazole</td>
<td>0.3-1.2% estimated absorption</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Mean peak 8.1 mg/L (~10% of oral peak)</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>60% of oral peak; AUC greater by vaginal route</td>
</tr>
<tr>
<td>Progesterone</td>
<td>50-100 mg can reach luteal phase plasma concentrations</td>
</tr>
<tr>
<td>MPA</td>
<td>½ to ¾ of concentrations achieved with depot MPA</td>
</tr>
<tr>
<td>Povidone-iodine</td>
<td>5-15-fold increase in serum iodine concentration</td>
</tr>
</tbody>
</table>
Cervical mucus in pregnancy