Dosing Principles and Dosage Form Considerations for BHRT

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• The following potential conflict of interest relationships are germane to my presentation:
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ZRT Laboratory is a testing Laboratory for hormones, cardiometabolic risks factors, Vitamin D

Objectives

• Discuss the popular dosage forms used for BHRT and the applications, advantages and disadvantages of each
• Review practical considerations to take into account with topical hormone preparations
• Discuss considerations in changing therapy from one route of delivery to another

In converting a patient who has been on CEE/MPA for years to bioidentical therapy:

a) Immediately stop MPA and start progesterone  
b) Immediately stop CEE and change to bi-est  
c) Increase bi-est dose until hot flashes are well controlled  
d) Stop CEE immediately but taper off MPA

What is the best dosage form for progesterone adminstration?

a) Oral Sustained Release Capsule  
b) Oral oil-filled capsule  
c) Sublingual toche  
d) Topical cream  
e) Topical gel  
f) None of the above
How often should a sublingual troche be administered

a) Once daily  
b) Twice a day  
c) Three times a day  
d) Every 2-3 hours  

Oral estrogen therapy results in:

a) Decrease in clotting risks  
b) Decrease in E2 to E1 ratio  
c) Decrease in CBG  
d) Decrease in TBG  
e) Decrease in SHBG  

Physiologic Bio-identical Hormone Restoration Therapy

• The goal of BHRT is to restore hormone levels to the normal physiological level of a younger individual to provide the protective benefits of the hormones to the entire system.

Dosage Adjustment

• Adjusting dosage for hormone restoration therapy individually requires assessment of therapeutic outcome and levels
  – Monitor symptoms
  – Retest to determine if physiological levels obtained

• If symptoms not resolved at normal physiologic levels, other causes should be considered:
  – Example: hot flashes with optimal estrogen levels: consider high cortisol, low thyroid, excessive progesterone, poor diet and exercise

Dosing Guidelines (Female)

• Peri-Menopause
  • Oral administration of SR capsules
    – Progesterone
      • 25 to 400 mg daily (usual 100 to 200 mg)
      • Dose once or twice a day
      • Give cyclically days 14 through 25
    – Bi-estrogen 50:50
      • If estrogen levels confirmed low
      • If progesterone alone doesn't control symptoms
      • 0.1mg to 0.5 mg daily
      • Dose once or twice a day
      • Give cyclically days 1 through 25
      • Continue progesterone as above

Continuous vs. Cyclic Dosing

• Hormones do not have to be given in cyclic fashion to provide benefits of restoration therapy
• Continuous dosing - take a break 2-5 days per month
Conversion to BHRT

• Considerations in conversion from synthetics to bio-identical hormones
  – No true equivalency
  – Length of time on synthetics
    • Estrogen receptors can lose sensitivity due to exposure to high amounts and/or long exposure of estrogen replacement (any type of estrogen)
  – Liver detox

• Taper off high estrogen dose
  – Elevated threshold in brain for estrogen
  – Withdrawal symptoms can be severe and highly individual

Conversion Considerations
Progesterone

• Progesterone affects estrogen effects
  – Regulates estrogen receptors
  – Has effects on SHBG, thyroid and cortisol actions — all effect "estrogen deficiency" symptoms

• Start progesterone prior to switching from synthetic estrogen to bio-identical estrogen
  – Discontinue any synthetic progestins

Conversion Considerations
Estrogen

• Taper off of synthetic estrogen
  – Higher than physiological levels reset the threshold for estrogen need within the brain
    • Quick reduction in dosage will cause withdrawal symptoms (severe hot flashes)
  – Various protocols
    • Example: decrease conventional estrogen therapy by one-half dose every 3 days, then 2 out of three days, then daily, etc
    • Example: Premarin — give ½ tab QD x 2 wks then ½ tab QOD x 2 wks
    • Use ½ dose every 3rd day for 9-12 days, then ½ dose 2 of 3 days for 9-12 days, then ½ dose daily, then ½ dose 2 out of 3 days for 9-12 days, then ½ dose every other day.
    – When low dose is reached, switch to Bi-est 50:50
      • Stronger ratio of E2 to E3 than Bi-est 80:20

Conversion Considerations
Estrogen

• Patient compliance
  – Let patient determine how quickly then can decrease dose
  – Patients on synthetics for a long duration may take longer to convert

• Dosage considerations
  – Start bio-identical estrogen dosage at mid-range
  – Difficult withdrawal usually requires higher dose of bioidentical
  – Consider changing estrogen ratio
    • Biest 40:60, 30:70, 20:80 (E3:E2)

Dosage Form Considerations
Converting Administration Routes

- Dosage comparisons difficult due to multiple influences on relative bio-availabilities
- Approximate ratio for topical:S/L: oral
  - For progesterone, estrogen, DHEA:
    topical 1: sublingual 2: oral 4-5
  - For testosterone: top 1: s/l 2: oral 5-6
  - Starting guideline only

Converting Administration Routes

- Switching to topical dosing may require higher initial dosing
  - Estrogen: 5-10 days
  - Progesterone and testosterone: 3 to 6 weeks
  - DHEA: ?
- Lab results may be confusing

Vaginal Administration

- Good absorption systemically
- Documented effectiveness for Progesterone in luteal phase defect
- Commercial products for Estrogens
- Used for systemic and/or local effects
- Dosage forms
  - Suppositories
    - Base MBK or Base A
  - Creams or gels
  - Vaginal troches

Oral Dosage Forms

General Considerations

- Micronized vs. non-micronized
  - Use source of consistent quality chemical
  - Size & percentage of micronization is critical
  - Higher production of metabolites

Oral Dosage Forms

- Immediate release capsules
  - 95% destroyed in upper GI tract before entering portal system
  - High peak increases risk of side effects
  - Would have to dose more frequently
  - No good reason to use
Oral Dosage Forms

- Sustained release capsules
  - Provides good level response
  - Less failures and side effects from “peak and valley” effect of other dosage forms
  - Easier to titrate dosage to an individual
  - Most women can dose once or twice a day
  - IJCP article validates use of Methocel E4M in compounded capsules to provide sustained release

Oral dosage forms

- Oil filled capsule
  - Absorption through lymphatic system bypasses GI destruction and first past effect to some degree
  - Not sustained release
  - May have to dose 2 to 4 times a day
  - More time consuming to compound
  - Prometrium®
    - Peanut oil base
    - 10% bio-available

Sublingual / Buccal Administration

- Advantages
  - Avoid upper GI tract destruction
  - Avoid first pass effect

Sublingual / Buccal Administration

- Disadvantages
  - May not get true sublingual absorption regularly
  - May have to dose more often
  - Taste may not be acceptable
  - May not be convenient to patient

Sublingual / Buccal Administration

- Drops
  - Vehicle choices
    - Aqueous suspensions or emulsions
    - Alcohol / Glycerin mixtures
    - Oils
  - Concentration
    - Flavor vs. convenience
      - Should use small volume, 0.2-0.25 max.
      - Concentrated taste harder to mask

Sublingual / Buccal Administration

- Pellet Implants
  - Requires surgical procedure and device
  - May cause infection or irritation
    - Surgery to remove
  - High “supraphysiologic” doses could occur
    - Initial “surge” then “fall off” effect
    - Too much may down regulate receptors
  - Implanted every 3-6 months usually
Pellet Implants

- May be optimal dosage form for elderly, non-compliant patient (Alzheimer’s)
- Expensive equipment required to compound
  - Limited number of compounders make pellets
- Some physicians report great clinical results

Topical Administration

- May take time to see full effect of hormones
  - May require “priming” with progesterone
  - May require patience with androgens
- Cream bases allow for more “depot” effect than “transdermal” or gel bases
  - Requires less total daily hormone dosing
- Transference of hormone is always a concern
- Cannot use serum or urine testing to see tissue (effective) level of hormone

Topical Administration of BHRT

- Steroids are low molecular weight, highly lipophilic molecules, therefore, good candidates for absorption across the skin
  - Use of a transdermal base not required for absorption

Topical Administration

Application considerations

- Skin “cement” and adipose tissue and may act as natural “reservoir” for hormones
  - Drained by the lymphatic system
  - “Depot” effect
- Target of application to skin should be lipophilic tissue, not the bloodstream
  - Use of a transdermal penetrating base may decrease depot effect of dosage applied

Permeability (Scheuplein Units-cm/hr)

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td>3.0 x 10^-6</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>3.0 x 10^-6</td>
</tr>
<tr>
<td>Estriol</td>
<td>4.0 x 10^-5</td>
</tr>
<tr>
<td>Estradiol</td>
<td>3.0 x 10^-4</td>
</tr>
<tr>
<td>Testosterone</td>
<td>4.0 x 10^-4</td>
</tr>
<tr>
<td>Pregnenolone</td>
<td>1.5 x 10^-3</td>
</tr>
<tr>
<td>Progesterone</td>
<td>1.5 x 10^-3</td>
</tr>
<tr>
<td>Estrone</td>
<td>3.6 x 10^-3</td>
</tr>
</tbody>
</table>

Increasing Permeability

Permeation of Steroids through Human Skin
Cream vs. Gel

- Emulsion cream bases without penetration enhancers added allow for more deposition to skin cement and fat storage sites.
- Compared to an equivalent dose in a gel base:
  - Somewhat slower absorption, longer activity
  - Takes longer to achieve symptom relief
  - Can accumulate to supraphysiologic levels if dosed too high
  - Will not see change in serum level
- Start dose higher than anticipated maintenance dose for a short time, then reduce.

Cream vs. Gel

- Gels contain the penetration enhancer alcohol.
- Compared to an equivalent dose in a cream base:
  - Somewhat faster absorption
  - Less deposition in skin cement and adipose tissue
  - Faster relief of symptoms
  - Less likely to accumulate with time
  - May see change in serum level
  - May have to dose higher and/or more often
    - Faster absorption, less depot, metabolized sooner
    - Repeated use has drying effect on skin.

Topical Administration

- Bases commonly used
  - Oil in water emulsions
    - Emollient cream base
    - Vanishing cream base
    - Combinations
  - Gels
    - Carbopol, HEC, HPC
    - Usually contain alcohol
  - Special “HRT” bases
    - Formulated for good absorption into skin
    - Absence of irritating and sensitizing agents

Topical Administration

- Maintenance dosage may be less than starting dosage.
- Method of application can vary degree of “depot” effect
  - Concentration
  - Volume (area covered)
  - Penetration properties of base
  - Solubility of drug

Topical Administration

Packaging considerations
- Accurate measurement of dosage
- Ability to adjust dosage
- Prevent contamination

Consultation considerations
- Compliance most important
  - Do not adjust dosage without supervision
- Accurate measurement
- Rub in well for at least one minute
- Caution on possible transfer of hormone to others
Injections
- High “supraphysiologic” doses given
  - High level initially followed by drop off until next dose
- Convenient?
  - Given much less often
  - Administered in doctor’s office
- Compounded products
  - Fixed Oil or Aqueous suspensions
  - Different salts/esters have different durations

Rectal Administration
- Good absorption
- Avoid 2/3rd of first pass effect
- Rectal suspension administered with syringe and rectal tip
- Inconvenient for patient
- Patient variability high

Oral vs. Topical Administration
- Topical administration of hormones is more efficient than oral
- Skin delivery is a more natural route of delivery

Oral Estrogen Therapy
- High conversion of estradiol to estrone
  - Giving enough oral estradiol to obtain a level in the low end of a normal pre-menopause level of estradiol will result in a corresponding elevated estrone level
  - Usually are not measuring estrone, and rarely measure estrone sulfate
  - Cannot mimic the natural ratio of estrogens with oral therapy

Oral vs. Topical Estrogens
- Oral E may reduce IGF-1 and increase GH levels
  - One study demonstrated transdermal does too
- Oral E may reduce postprandial lipid oxidation
  - Reduction in lean mass and increase in fat mass
- Transdermal E lowers antithrombin III levels—which are associated with severe and recurrent venous thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Serum E2 (pg/ml)</th>
<th>Serum E1 (pg/ml)</th>
<th>E2/E1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopause</td>
<td>60</td>
<td>60</td>
<td>1</td>
</tr>
<tr>
<td>Postmenopause</td>
<td>20</td>
<td>60</td>
<td>0.33</td>
</tr>
<tr>
<td>Oral Estradiol</td>
<td>60</td>
<td>300</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Estradiol (E2), Estrone (E1) and Oral Estrogen Supplementation
Oral vs. Topical Estrogens

- Oral administration of estrogen increases HDL but also increases triglycerides
- Topical estrogen shows no changes in HDL or triglycerides
- Both routes of E reduce LDL, VLDL, and Lp(A),
- Topical estrogens improve appearance and function of skin

Oral vs. Topical Progesterone

- Oral Progesterone produces more metabolites than topical
  - Larger dosage required because of loss of 90-95% with GI destruction and first pass effect
  - Allopregnenolone works on GABA receptor
    - Sedative and hypnotic properties
  - Different metabolites produced - some that inhibit and some that increase cancer tumor growth
- Topical progesterone may also increase appearance of skin

Topical Hormones

- Topical testosterone may increase hair density and growth (where you don’t want it)
- Not much is known about the metabolism of hormones that may occur in the skin
  - Never been shown to be a significant effect

Dosage Form Considerations

Summary

- Oral route should utilize SR and consistent source of micronized hormone
  - Will increase metabolites compared to other routes
- S/L or Buccal will require more frequent dosing
  - Cannot use saliva testing of free hormones
- Injections cause peaks and troughs of hormones and metabolites
- Topical route results in less metabolites
  - Cannot use urine or serum testing to adjust
- Most important factor in choice is patient compliance

Relative Potency of Estrogens

- Estradiol (E2) is 12x more potent than estrone (E1) and 80x more potent than estriol (E3)
  - ......as measured by action on the uterine tissue.
- Vaginal/Urogenital tissue responds better to estriol
- Estradiol estimated by some to be 1000x more potent in regards to proliferative effect
The three major estrogens produced by our bodies:
- Estrone (E1)
- Estradiol (E2)
- Estriol (E3)

Considerations in Estrogen Replacement Therapy

Bio-identical Estrogens

Original Formulations (80% Estriol)

Human Estrogen

<table>
<thead>
<tr>
<th>Tri-Est (original) 1.0 mg</th>
<th>Tri-Est 0.2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol 0.1 mg (10%)</td>
<td>Estradiol 0.05 mg (25%)</td>
</tr>
<tr>
<td>Estrone 0.1 mg (10%)</td>
<td>Estrone 0.05 mg (25%)</td>
</tr>
<tr>
<td>Estriol 0.8 mg (80%)</td>
<td>Estradiol 0.1 mg (50%)</td>
</tr>
</tbody>
</table>

Biest Formulas

- There is NO standard ratio
- Prescribe/label in a manner that clearly indicates your intention or preparation
  - Ex: Biest: E2 0.1 mg/E3 0.1 mg or
  - Ex: Biest 0.2 mg (E2 0.1/E3 0.1)
- Prescribe/label individual amounts
  - Avoid percentages!

The Influence of Estriol

The Influence of Estriol

**E3:E2**
- 1.0 mg Bi-est 80:20
- 0.4 mg Bi-est 50:50

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Thanks For Listening!!!

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