Systemic Estradiol Levels with Low-Dose Vaginal Estrogens May Differ by Dose and by Product

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Objective

To review systemic E2 levels with various low-dose and ultra-low-dose vaginal estrogens measured by various methods, and evaluate basal levels of E2 reported in normal, untreated postmenopausal women

Methods

• A review of E2 absorption with vaginal estrogens was published in 2015. We have updated data of that review by searching for relevant studies of low-dose products reported since that publication. PubMed was searched in July 2018 for the past 5 years for pharmacokinetic studies that measured systemic E2 levels in postmenopausal women using combinations of biomarkers that included estradiol, estrone, conjugated estrogens, dehydroepiandrosterone (DHEA), pregnenolone, androstenedione, androstenedione, and dehydroepiandrosterone sulfate (DHEAS).
• Studies were excluded if E2 levels were measured in women taking aromatase inhibitors or antiestrogen therapy. GC/MS/MS and LC/MS/MS methodologies quantify systemic E2 as low as 0.5 pg/mL to 3 pg/mL.
• Despite minimal systemic absorption of estradiol with vaginal estrogens, approved vaginal estrogen therapies are required to include a boxed warning section (“black box”) similar to systemic estrogen therapies.

Conclusions

• Consistent with our previous reviews, systemic E2 levels in postmenopausal women from studies of vaginal estrogens vary by assay and estrogen dose.
• Systemic E2 levels in postmenopausal women with various low- and ultra-low-dose vaginal estrogen therapies vary by assay and estrogen dose and product.
• Women with low-dose estrogen therapy have lower systemic estrogen exposure than women receiving ultra-low-dose estrogen therapy,

Table 1. Mean Systemic E2 Levels at Baseline and Throughout Vaginal Estrogen Studies by Assay Type and Dose

<table>
<thead>
<tr>
<th>Assay Type</th>
<th>Estradiol (pg/mL)</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Mean Basal E2 Levels in Postmenopausal Women Measured with Mass Spectrometry</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC/MS/MS</td>
<td></td>
<td></td>
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<tr>
<td>Plasma</td>
<td>4.9 ± 0.3</td>
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<tr>
<td>Permenopausal</td>
<td>4.6 ± 0.2</td>
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<tr>
<td>LC/MS/MS</td>
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<tr>
<td>Plasma</td>
<td>3.5 ± 0.2</td>
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<tr>
<td>Permenopausal</td>
<td>3.0 ± 0.1</td>
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<td>RIA</td>
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<tr>
<td>Plasma</td>
<td>3.2 ± 0.1</td>
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<tr>
<td>Permenopausal</td>
<td>2.9 ± 0.1</td>
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References