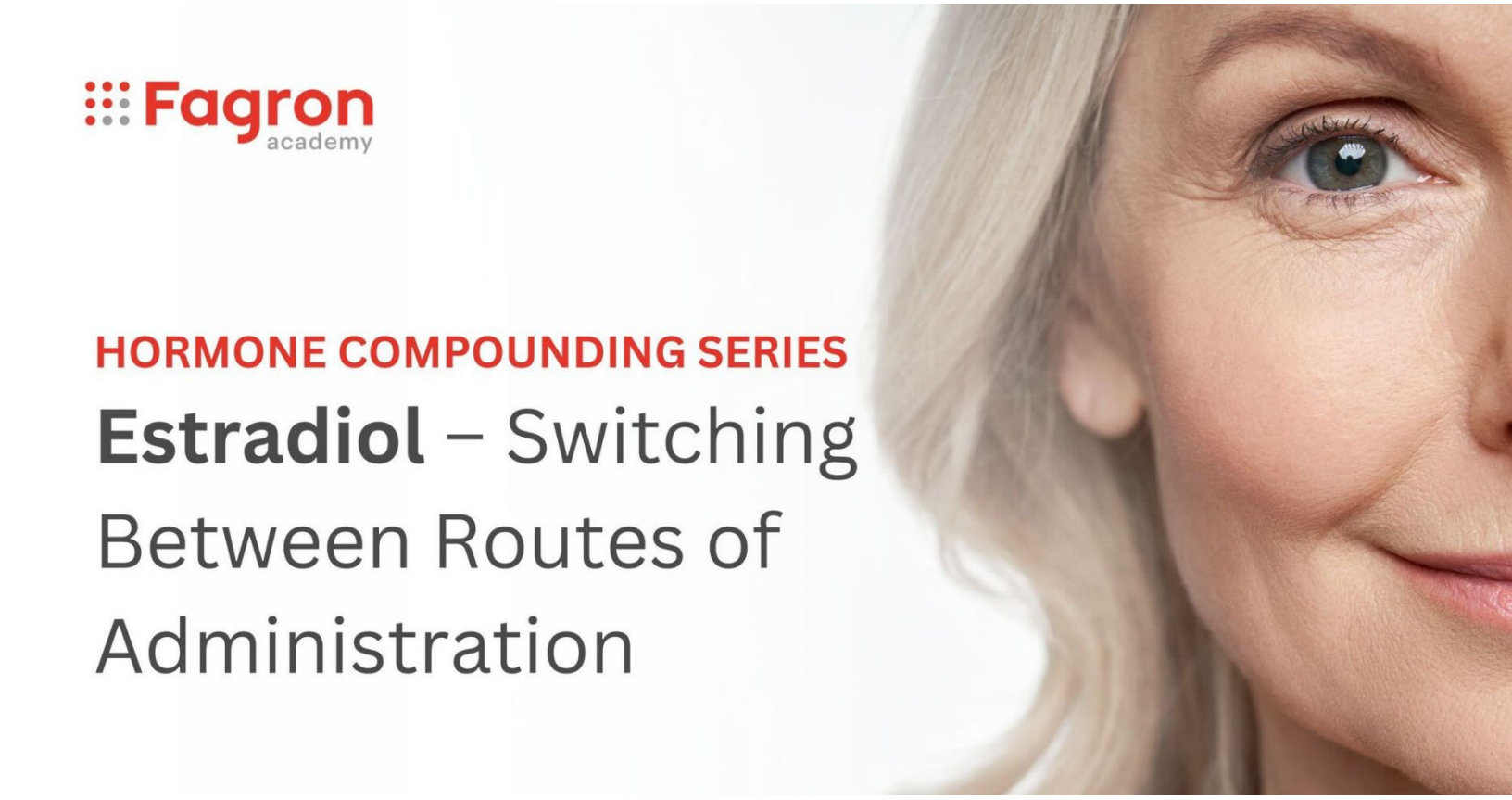

HORMONE COMPOUNDING SERIES

Estradiol – Switching Between Routes of Administration

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Estimates from the American College of Obstetricians and Gynecologists report menopausal related symptoms, such as vasomotor symptoms, impact 50-82% of women in the US going through menopause.[1]

Currently, systemic estrogen hormone replacement therapy, with or without a progestin, is thought to be the most effective therapy for menopause-related vasomotor symptoms.[2] Low estrogen is thought to be a trigger for symptoms such as hot flashes (vasomotor symptoms), vulvovaginal atrophy, vaginal dryness, and dyspareunia among others. For women with an intact uterus, treatment with a progestin is necessary to protect the endometrium from hyperplasia and associated risks.[3]

Despite the utility of hormone replacement therapy for the management of vasomotor symptoms, previous data from the Women's Health Initiative (WHI) indicating the risks of hormone replacement therapy (HRT) resulted in significant declines in HRT prescribing in the US, Canada, and the UK, among other countries.[5] Recent literature, such as a review published in JAMA in May 2024, put the data from the WHI study into context by indicating that the study was primarily in women in late menopause (over the age of 60). It also focused on HRT for chronic diseases such as cardiovascular disease or dementia rather than its utility for vasomotor symptoms.[5,6]

The JAMA review concludes that, though the WHI data recommends against the use of HRT in older women for prevention of chronic diseases, treatment of women in early menopause for vasomotor symptoms is appropriate outside of specific contraindications.[6] This recent change in rhetoric on HRT may result in changes in prescribing practices, resulting in a need for education on the different routes of administration for HRT, why

a patient may choose one over another, and a need for information on switching between routes of administration.

Why Switch Between Routes?

There are a variety of estradiol products available on the market specifically for management of menopause related symptoms, including transdermal gels, sprays, patches, vaginal creams and tablets, and oral tablets, and injectables, among others. Patients may switch between these therapies or compounded options for a variety of reasons including adverse event profile, issues with application (for example, transference associated with topical/transdermal use), or convenience/ease of use.

Compounded preparations may be indicated for patients with allergies to existing commercially available products, or for those who need treatment with several hormones and are looking to avoid the need to use multiple different products. Compounding may also be an option for patients who fail to achieve appropriate symptomatic control and levels on dosages that can be easily measured with these commercially available products.

With regards to adverse event profile, estradiol supplementation via different routes is associated with different risks. Though overall the risk remains low, oral estradiol is associated with increased venous thromboembolism (VTE) risk, whereas transdermal estradiol was not found to be associated with significant increased risk of VTE.[7]

The reason for the discrepancy is thought to be the result of procoagulant factors being formed as a result of first pass hepatic metabolism for estradiol, a factor that doesn't apply to the transdermal route.7 Though specific data on VTE risk for other routes of administration that bypass or partially bypass hepatic metabolism (such as the buccal or sublingual routes) is not available, it has been hypothesized that these routes may also result in decreased risk of VTE compared to the oral route.[8]

Another impact of oral estradiol given its hepatic metabolism is an impact on angiotensinogen. Oral estrogen is thought to undergo first pass hepatic metabolism resulting in activation of the renin angiotensin aldosterone system which subsequently increases levels of angiotensin II. Angiotensin II is a vasoconstrictor and may be associated with increased blood pressure, though, the overall risk of this is unclear.

Studies of some oral estrogens, such as conjugated equine estrogens (CEE) have shown an increase risk of hypertension compared to placebo with long-term use. Data from one large prospective population-based study concluded that oral estrogens were associated with an increased risk of hypertension compared to transdermal or vaginal estrogens. Furthermore, conjugated equine estrogens were associated with a higher risk than estradiol.[9] Given the differential impact, women with already high blood pressure may prefer transdermal or vaginal estradiol over oral estradiol options if they are otherwise indicated for HRT.[10]

Though comparative data on the injectable route of administration is limited, one study looking at various types of estrogen and routes of administration with estrogen in menopausal women between 2007 and 2020 found a significantly increased risk of ischemic heart disease among patients using injectable estradiol valerate over other routes of administration such as oral or transdermal use. Additionally, though other routes of administration were associated with a modest reduction in heart failure risk, high dose injectable estrogen therapy (defined by the study as 1.45x above standard dose of 10-20mg every 4 weeks) was instead associated with an increased risk.[11]

Dosing considerations for switching between routes of administration

When a patient is switched from one route of administration to another, finding the correct dosing can be a challenge. Frequently, dosage adjustment and monitoring may be needed to find the correct and efficacious dose upon switching. Though set guidelines for switching between routes of administration in terms of how to

convert dosing are not available (to my knowledge), we can use data on pharmacokinetic parameters such as bioavailability to help guide our approximate starting dose selection.

For example, due to the impact of first pass metabolism, some studies suggest approximately 5x greater bioavailability via the buccal route as compared to the oral route of administration. Studies have found vaginal estradiol administration to result in 10 fold higher serum levels compared to the same dose orally.10 One study that looked at 2mg and 0.2mg estradiol vaginally found the higher dose resulted in a rapid serum level of 530pg/mL whereas the 0.2mg dose increased serum level to 80pg/mL, with the 80pg/mL being similar to serum levels noted in other studies consistent with a 2mg oral dose.[10,12]

Transdermal estradiol may vary by application type, but one study of the gel found that treatment with 1.5mg estradiol transdermal gel produced similar levels to 2mg estradiol orally or 0.2mg vaginally, suggesting about 75% of the dose is needed transdermally as compared to orally.10 The package inserts for oral and transdermal estradiol products do not specify monitoring timelines, though transdermal estradiol has been shown to take as long as 12 to 14 days to reach steady state in some studies whereas oral estradiol achieves steady state more quickly at around 5-6 days.[13] Specific information on pharmacokinetics for estradiol administered buccally were unavailable, though, one study reported steady state had been achieved after two weeks of treatment.[10]

A note on estradiol vs estriol vs conjugated equine estrogens

Though estradiol is the predominant estrogen used for control of vasomotor symptoms in menopausal and postmenopausal women it is sometimes used in combination with other estrogens such as estriol or conjugated equine estrogen products, such as Premarin, are sometimes used in place of estradiol.

Estriol is typically found in low amounts in non-pregnant women. It acts as a weak estrogen in tissues such as the endometrium and liver but offers stronger estrogenic activity vaginally. Some of this weaker activity

may be due to its rapid dissociation from the activated receptor as compared to estradiol.10 The benefit of this more localized estrogenic action is a decreased impact of vaginal estriol for management of vaginal dryness on the endometrial tissue as compared to other estrogens such as estradiol. One study found that a regimen of 0.5mg vaginal estriol daily for 2 to 3 weeks followed by twice weekly administration for a period of 2 years did not result in endometrial proliferation.[14] Many of the studies currently available evaluate estriol specifically via the vaginal route, though, it is sometimes compounded via the oral or transdermal routes as well.

Conjugated equine estrogens are a mixture of sodium estrone sulfate and sodium equilin sulfate among other estrogenic substances derived from pregnant mare urine or synthetically derived.15 Conjugated equine estrogens 0.625mg orally is thought to approximately correspond with the estrogenic effect of 1-2mg estradiol orally.10 Some studies suggest that oral CEE may be more prothrombotic and have a greater impact on blood pressure as compared to other estrogens such as estradiol.[9,16]

Interested in compounding topical, transdermal, or vaginal estradiol? Check out our recent stability study published in the International Journal of Pharmaceutical Compounding: International Journal of Pharmaceutical Compounding (ijpc.com) and sign up for our Webinar Understanding HRT for Women: A Practical Guide to Interpretation of Lab Results

For further information or questions, please feel free to reach out to us by heading to www.fagronacademy.us!

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