Pharmacokinetics of the First Combination 17β-Estradiol/Progesterone Capsule in Clinical Development for Hormone Therapy

James H. Pickar, M.D. 1, Charles Bon 2, Julia M. Amadio 3, Brian A. Bernick, M.D. 3
1Columbia University Medical Center, New York, NY; 2Biostudy Solutions, Wilmington, NC; 3TherapeuticsMD, Boca Raton, FL

INTRODUCTION

- No FDA-approved combination product containing the natural hormones, 17β-estradiol and progesterone, exists.
- Combining 17β-estradiol and progesterone as a product with good bioavailability is difficult to achieve biochemically.
- Compounding pharmacies attempt to manufacture this combination, but such compounding should be viewed with caution.
  o Progesterone has poor bioavailability.
  o The proper route of progesterone to estradiol in a combination formulation is difficult to achieve.
- In two FDA surveys of compounding pharmacies, the amount of hormone contained in compounded products was not the amount claimed in approximately 34% of compounded products and 28% of hormone samples versus the USP routinely found for commercially manufactured products.
- Pharmacokinetic studies of compounding pharmacy products are rarely performed.
- Progesterone levels in women taking compounded progesterone may not be sufficient for endometrial protection from estrogen stimulation.
- The investigational product (TX-12-0001-HR) is the first oral combination 17β-estradiol/progesterone capsule (TherapeuticsMD, Inc., Boca Raton, FL) being studied for regulatory approval, and is the first progesterone-containing combination without peanut oil. The progesterone and estradiol contained in the combination are chemically identical to the hormones of the human ovary.
- Under FDA guidance for 505(b2), relative bioavailability of any new product needs to be compared with the approved reference products, which for estradiol and progesterone are Estrasert and Promomet, respectively.

OBJECTIVES

- To determine the pharmacokinetics (PK) and oral bioavailability of a combination capsule of 17β-estradiol and progesterone (Test drug, TX-12-0001-HR).
- To compare Test drug PK and bioavailability with that of widely used individual formulations of the same Estradiol (Estrasert USP 2 mg), Testosterone (Testosterole, 2 mg), Estradiol (Promomet, 2 mg), and Progesterone (Progesterone oral capsule 200 mg) marketed by Estrogen Pharmaceuticals, Inc., Parkland Laboratories, respectively.
- To compare Test drug PK and bioavailability with that of widely used individual formulations of the same other marketed estrogen and progesterone products.

SUBJECTS AND STUDY DESIGN

Subjects
- Male inclusion criteria: Healthy postmenopausal women aged 45 to 60 years with a BMI 19.5 to 29.9 kg/m² who were non-smokers or ex-smokers (no smoking in the last 3 months).
- Male exclusion criteria: Smoking, gastrointestinal problems, or any health problems within 60 days before and throughout the study, use of any hormone agonist or antagonist for 13 days before the study, and use of oral or injectable hormone therapy within 3 months before dosing.

Study design
- Open label, parallel randomized, single-site, 2 treatment, 3 period, 3 sequence, crossover, partial replicates, reference scaled, oral, million women bioavailability study.
- Patients were randomly assigned sequentially to 1 of 3 dosing sequences of the same dose of Test drug (T) and Reference products (E 200 mg, thrice weekly).
- 24 blood samples were collected at multiple intervals from 1 h to 48 h to relay dosing.

RESULTS

Subject disposition and baseline characteristics
- 56 subjects were randomized and 52 (92.9%) completed the study (Figure 1).
- Subjects had a mean age of 54 ±5.6 years (range 44-69) and a mean BMI of 26.8 ±3.9 kg/m² (range 18-719).
- Relative bioavailability results
- All AUC and Cmax parameters meet the bioequivalence criteria for all analyses, except Cmax for total estradiol (Table). The extent of estradiol and progesterone absorption for the Test capsule appeared to be similar to that for the Estradiol and Promomet tablets, respectively.
- The rate of estradiol absorption (Tmax) for the Test capsule appeared to be slightly faster than that for Estradiol.
- Georgiades et al. also found for each analysis were presented in Figures 2-3.

CONCLUSIONS

- The combination 17β-estradiol/ progesterone product (TX-12-0001-HR) demonstrated bioavailability of its constituents similar to that of its respective references of Estradiol and Promomet, when the reference products were given together under fed conditions.
- The relative bioavailability results would suggest the Test capsule containing natural progesterone and estradiol should have the same safety profile as that of the two reference products, Promomet and Estradiol, taken together.
- This new investigational therapy, if approved, would represent an exciting development in hormone therapy, as no approved hormone therapy drug has been able to:
  1) Combine natural progesterone with 17β-estradiol as an oral formulation, and
  2) Offer the additional advantage of avoiding the use of peanut oil, a known allergen.

References

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