In Vitro Percutaneous Absorption of Extemporaneously Compounded Estradiol Formulations

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INTRODUCTION:

Extemporaneously compounded bioidentical hormones are commonly dispensed in the United States. Estradiol (E2) and Estriol (E3) replacement therapy is often recommended when female patients present with lower than normal physiologic levels, such as patients going through menopause. Estradiol may be administered alone or in combination with other hormones, typically in vaginal or topical dosage forms. Despite its widespread use, questions have been raised regarding the safety, effectiveness and use of compounded hormone replacement therapy (cHRT).

There is a need for clinical and scientific evidence on cHRT, in particular regarding topically applied hormones.

METHODOLOGY:

A validated *in vitro* study was conducted to evaluate the human skin percutaneous absorption of topically applied estradiol, using the Franz Skin Finite Dose Model. An aqueous compounded cream (VersaBase Cream) and an anhydrous compounded gel (VersaBase Anhydrous HRT) were prepared for estradiol 0.06%, and also for estradiol 0.06% / estriol 0.1% (E2/E3, biest). The commercial medication ESTROGel (estradiol 0.06%) was used as positive control. The compounded formulations were applied on three female skin samples and the corresponding hormone concentrations were determined by ELISA. The mean flux rate and the total percutaneous absorption were calculated for all samples.

RESULTS & DISCUSSION:

The aqueous and anhydrous extemporaneously compounded formulations exhibited similar rate of absorption (permeation profile), characterized by a steady mean flux that increased slightly up to around 8 hours, and decreased slightly towards the end of the study (24 hours). The ESTROGel, on the other hand, exhibited a quick rise in skin percutaneous absorption to a peak at approximately 1 hour after dose application, followed by a quick decline in flux over time (up to 4 hours), and then decreased slightly as well towards the end of the study. The permeation profiles of estradiol from the compounded formulations were statistically significant different to ESTROGel. When extrapolated to the clinical practice, it seems that the compounded formulations will provide a more steady delivery of estradiol, comparable to what is to be expected *in vivo*.

Upon 24 hours of topical application, the mean cumulative absorption of estradiol for biest anhydrous compounded gel, estradiol anhydrous compounded gel, biest aqueous compounded cream, estradiol aqueous compounded cream and ESTROGel was 213.6±109.5 ng/cm^2, 209.8±121.4 ng/cm^2, 255.8±138.5 ng/cm^2, 319.8±107.1 ng/cm^2 and 280.0±116.7 ng/cm^2, respectively (Figure 1).

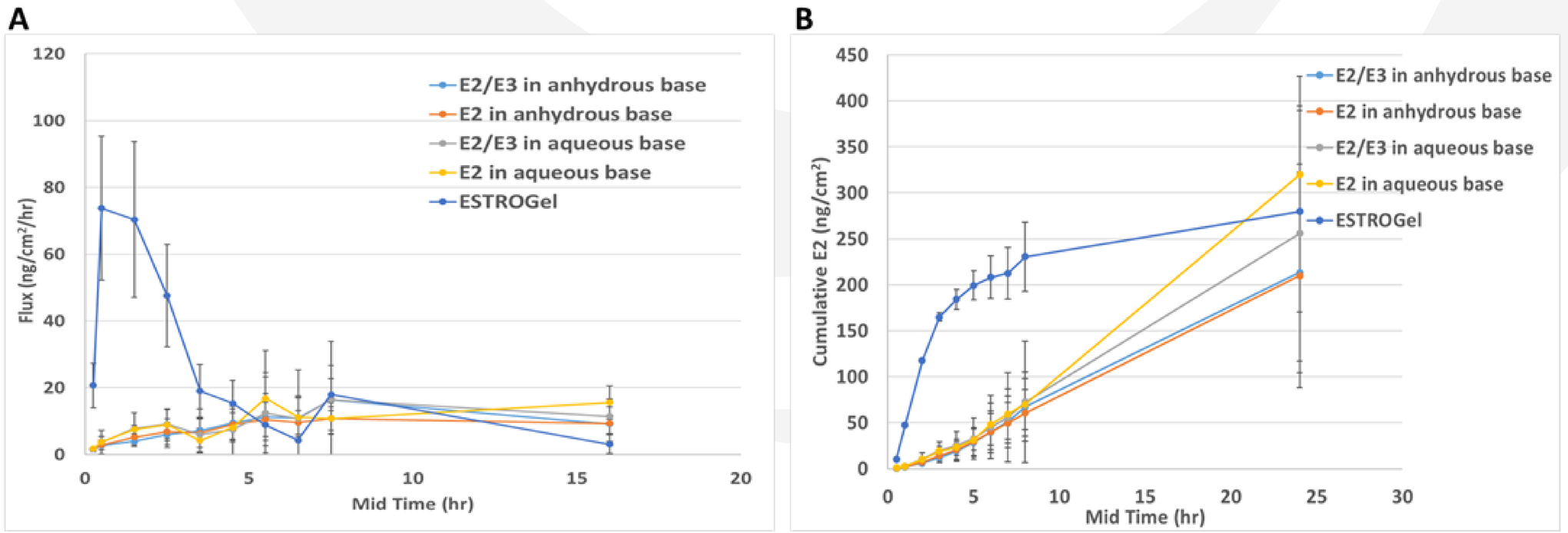

Figure 1.
Mean flux rate (A, left) and total percutaneous absorption (B, right) of estradiol compounded formulations in the aqueous and anhydrous topical bases, in comparison to the commercial medication ESTROGel.

CONCLUSIONS:

It is demonstrated that estradiol penetrates through the skin upon topical application of aqueous and anhydrous compounded formulations. These results are important evidence to support the effectiveness of cHRT since the in vitro model used has proven to accurately predict in vivo permeation kinetics.