

CDER Internal Dermatopharmacokinetic Study

Objectives

- 1) Evaluation of skin stripping methodology to study dermatopharmacokinetics (DPK) of topical products in the stratum corneum (SC) of human subjects.
- 2) To determine the time and resources needed to establish the skin stripping methodology in a new laboratory.

Background

This internal three-part feasibility study used methods developed at the University of Utah where the FDA sponsored bioequivalence study was conducted. Results were directly compared with the Utah study. Focus was on three 0.025% tretinoin gel products currently on the market. The two brand names Retin-A® Gel by Johnson and Johnson (Reference Listed Drug) and Avita® Gel by Bertek Pharmaceuticals have different formulations while the generic product by Spear Pharmaceuticals is qualitatively and quantitatively similar to Retin-A® Gel. The FDA investigators had no prior experience in conducting any DPK studies in human skin.

Part 1: Validation Study

This study was intended to seek out sources of variability. Prior to dosing, data was collected on the weight of SC removed by tape strips and the weight of the drug product applied to the skin. After dosing, data was collected on the amount drug product that was recovered in SC. Relative disposition of each drug product in different layers of SC was also determined. The SC concentrations of tretinoin and its pharmacologically active isomer, isotretinoin were measured by a validated HPLC method.

Study design:

Forearms of six subjects were washed with Purpose® gentle liquid soap, gently wiped and allowed to dry for 1 h. Retin-A® gel (5 µL) was applied for 1 hour on 4 sites (1.13 cm² surface area/site) per arm for each subject. Tape strip #1 was discarded. Tape strips # 2-10 were extracted to quantitate tretinoin and isotretinoin. In the disposition study strip #1, strips #2-10 and additional strips #11-20 were extracted.

Results:

- 1) The FDA and Utah studies were comparable with respect to the weight of SC removed and the amount of gel applied. The intra-arm variability was comparable in both studies.
- 2) The amounts of tretinoin and isotretinoin recovered from the skin strippings were 2 times higher in the FDA study compared to the Utah study.
- 3) In the gel disposition experiments, excess of tretinoin and isotretinoin concentrations was recovered in the first strip while a gradient was seen across strips 2 to 20 for all three formulations.

4) Penetration of Avita® gel in the SC appeared to be slower than the other gel products.

Part 2: Pilot Study

This study was conducted to measure the tretinoin and isotretinoin concentrations from Retin-A® gel over a period of time. The drug profiles were used to determine pharmacokinetic parameters, C_{max} , T_{max} , and AUC_t .

Study Design:

Forearms of five subjects were washed and dried as before. Retin-A® gel (5 µL) was applied on 4 sites (1.13 cm² surface area/site) each on the left and right arm corresponding respectively to 0.25, 0.5, 1, 1.5, 3, and 4.5, 7.5 and 10.5 h sampling. In addition 1 site on each arm was used as untreated controls (pre-dose sampling). Residual drug was removed from all sites at 1.5 h. and sampling was continued. At each sampling point, tape strip #1 was discarded while tape strips #2-10 were harvested and extracted.

Results:

- 1) None of the subjects had measurable drug concentrations at 0 hour.
- 2) Mean C_{max} values in the FDA study were comparable with the Utah study.
- 3) Mean T_{max} values in the FDA study were delayed and variable compared to the Utah study.
- 4) Only the uptake phase of FDA study was comparable with the Utah study.
- 5) The elimination phase was not well defined in the FDA study.

Part 3: Pivotal Study

The study was conducted to determine the feasibility of comparing the three formulations simultaneously using the DPK approach. Tretinoin and isotretinoin concentrations from three gels were measured over a period of time. The study was not powered to determine the bioequivalence.

Study design:

Forearms of two subjects were dried as before. Five microliters each of Retin-A®, Spear and Avita® gels were applied in a blinded manner on 10 sites (1.13 cm² surface area/site) each on the left and right arm corresponding respectively to 0.25, 0.5, 1, 1.5, 3, and 4.5, 7.5 and 10 h sampling. In addition 1 site on each arm was used as untreated controls (pre-dose sampling). Residual drug was removed and sampling was continued as in the pilot study. At each sampling point, tape strip #1 was discarded while tape strips #2-10 were harvested and extracted.

Results:

- 1) T_{max} was delayed in case of Avita® gel. The SC concentrations of tretinoin and isotretinoin reached C_{max} around 1 hour for Retin-A® and Spear gels and at 1.5 hours for Avita® gel.

- 2) The uptake phase of FDA study was comparable with the Utah study.
- 3) During uptake phase, SC concentrations of tretinoin and isotretinoin from Avita® Gel were about 50% of those from Retin-A® and Spear Gel products in the FDA study. This observation correlated with the Utah study.
- 4) The elimination phase was prolonged in the FDA study.

Conclusions

- 1) The skin-stripping methodology can be easily transferred and results are reproducible in another laboratory.
- 2) The time and resources needed for the transfer of skin stripping and DPK methodology are reasonable.
- 3) The DPK method has the potential to detect formulation differences in topical products.

References

- 1) Draft Guidance for Industry: Topical Dermatological Drug Product NDAs and ANDAs-In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies, June 1998.
- 2) Guidance for Industry: Bioanalytical Method Validation, May 2001.