A Comparison of the *In Vitro* Permeation Test versus the Vasoconstrictor Assay in Assessing Topical BA/BE

Paul Lehman [1] and Thomas Franz [2]

[1] QPS-LLC, One Innovation Way, Suite 200, Newark, DE 19711 [2] Retired

INTRODUCTION

The long history of use of excised human skin as an accepted *in vitro* model for the study of percutaneous absorption has logically led to its consideration as a surrogate for clinical trials or human pharmacokinetic studies in determining the bioavailability (BA) and bioequivalence (BE) of topical drug products. The purpose of this study was to compare the sensitivity of the *in vitro* permeation test with that of an already accepted surrogate test, the human skin blanching or vasoconstrictor assay, in assessing the relative bioavailability of topical clobetasol propionate products.

MATERIALS AND METHODS

The percutaneous absorption of clobetasol propionate from five commercial products was measured *in vitro* using cryopreserved human skin from fourteen donors. Skin sections were mounted onto 0.8 cm^2 Franz diffusion cells and dosed with approximately 5 mg of product. Clobetasol absorption was assessed by sampling the dermal receptor solution at 4, 8, 12, 24, and 48 hours, and quantifying drug content by HPLC. The same five products were also assessed *in vivo* using the vasoconstrictor assay. Product was applied to 3.1 cm^2 areas on the ventral forearm of forty-eight subjects. Skin blanching was assessed at 0, 1, 2, 3 , 8, 12, 24, and 30 hours post-dose removal (Dose duration = 3 hours) using a Minolta Chroma Meter. The data were quantified as the area-under-the-blanching curve.

RESULTS

The *in vitro* permeation test found total clobetasol absorption varying ten-fold from highest to lowest product, whereas the vasoconstrictor assay found this same difference was less than two-fold. The coefficient of variation ranged from 78-126% in the vasoconstrictor assay, but only 30-43% in the *in vitro* skin permeation test. Statistically, the permeation test could separate the 5 products into three groups: 1) ointment, 2) cream and gel, 3) emollient cream and solution. Due to its greater variability as well as saturation of the pharmacodynamic response at higher flux levels, the vasoconstrictor assay found all products except the solution to be equipotent.

Figure 1. Rate of CP IVPT absorption from Ointment (▲) , Gel (▶), Cream (■), Solution (●), and Emollient Cream (▼).

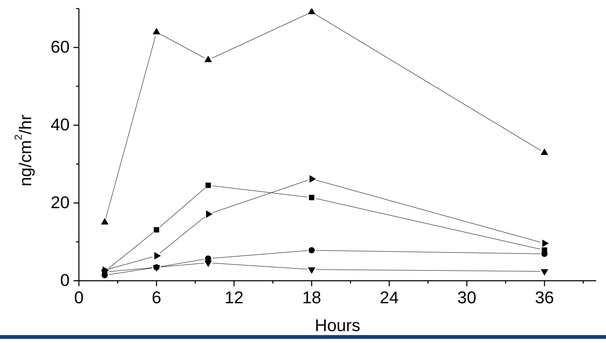

Figure 2. Vasoconstrictor response measured as change in mean corrected a* scale following product application (n=48).

Ointment (▲) , Gel (▶), Cream (■), Solution (●), and Emollient Cream (▼)

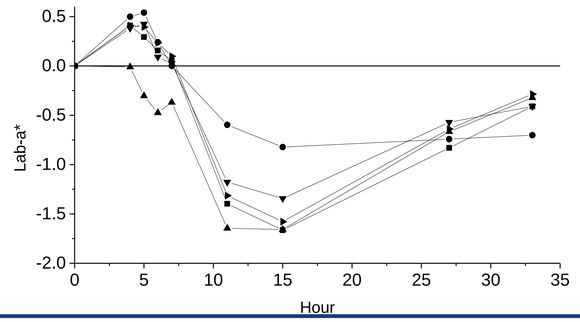

Figure 3. Negative AUEC versus rate of CP absorption for the time interval 8 – 12 hours. Solid line represents the best fit of the data using the E-max model. (Mean ± SE)

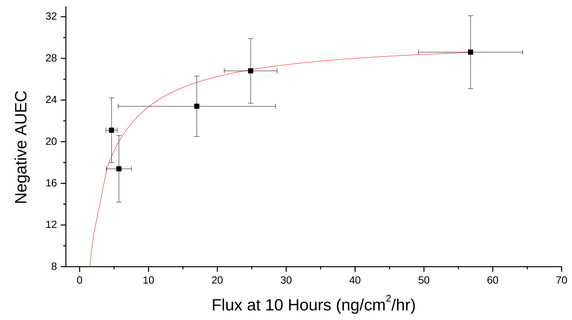

Table 1. Summary of CP *in vitro* Permeation Data

Product	# Skin Sections/ # Donors	Total Absorbed (% Dose/48 hr)	Relative BA
Ointment	12/4	62.3 ± 9.0	3.3 ± 0.4[a]
Gel	12/4	20.8 ± 3.6	1.5 ± 0.2[b]
Cream	50/13	18.0 ± 1.8	1.00[b]
Solution	30/6	10.3 ± 1.7	0.52 ± 0.1
Emollient Cream	20/6	4.3 ± 0.7	0.31 ± 0.1

Data presented as Mean ± SE
a. Significantly different from all other products
b. Significantly different from ointment, solution, and emollient cream

Table 2. Summary of CP Vasoconstriction (VC) data.
For comparison the variability observed in the *in vitro* permeation test (IVPT) is also given.

Product	AUEC	CV (%) VC Assay	CV (%) IVPT
Ointment	-28.6 ± 3.5 [a,b]	82	30
Cream	-26.8 ± 3.1 [a,b]	78	35
Gel	-23.4 ± 2.9 [a]	84	36
Emollient Cream	-21.1 ± 3.1 [a]	100	43
Solution	-17.4 ± 3.2 [a]	126	39
BMV Lotion	-5.3 ± 3.0	---	---

Data presented as Mean ± SE
AUEC = area under the effect (blanching) curve, CV = coefficient of variation
a. Significantly different from BMV Lotion
b. Significantly different from solution (Scalp Application)

CONCLUSIONS

These data document the remarkable sensitivity of the *in vitro* permeation test and strongly support its use for the determination of BA and BE of topical drug products.

AAPS 2014 - Correspondence: paul.lehman@qps.com Tel: +1 253.447.8932