Characterization of the Human Skin Percutaneous Absorption of Lorazepam using the Franz Finite Dose *in vitro* Permeation Test Model

Daniel Banov
Gus Bassani
Bryan Prescott
Maria Carvalho

PCCA
9901 South Wilcrest Drive
Houston, TX 77099
USA

PAINWEEK®

Purpose

The human skin percutaneous absorption of transdermal compounded formulations containing lorazepam incorporated in the proprietary bases Lipoderm and Lipoderm ActiveMax, was evaluated using the Franz Finite Dose *in vitro* Permeation Test Model (IVPT). Lorazepam is an anxiolytic, sedative, hypnotic and antipsychotic drug commonly prescribed by physicians to relief anxiety and restlessness. When the oral route of administration is compromised (e.g. hospice care), topical lorazepam represents a viable alternative provided that the drug is absorbed transdermally. The Franz Finite Dose IVPT Model has proven to be a valuable tool for the study of percutaneous absorption and determination of the pharmacokinetics of topically applied drugs. It has also proven to accurately predict *in vivo* percutaneous absorption kinetics since this model uses *ex vivo* human torso skin mounted in specially designed diffusion chambers allowing the skin to be maintained at a temperature and humidity that match normal *in vivo* conditions. Therefore, the Franz Finite Dose IVPT Model was selected to characterize the percutaneous absorption of lorazepam into and through the skin by evaluating the total absorption, rate of absorption and the skin content of lorazepam applied to the outer surface of the skin.

Methods

The percutaneous absorption of lorazepam was measured using *ex vivo* human torso skin samples, without obvious signs of disease, from two male and one female donors (Hispanic and Caucasian races). The skin samples were dermatomed, cryopreserved, sealed in a water-impermeable bag and stored at approximately -20°C prior to use. The skin samples were then rinsed in water and cut into small sections to fit on nominal 2.0 cm^2 diffusion cells (Figure 1). The dermal (receptor) chamber was filled to capacity with a receptor solution. The integrity of each skin section was evaluated by testing its permeability to titrated water prior to the experiment.
Lorazepam 5 mg/g was incorporated in Lipoderm and also in Lipoderm ActiveMax and each compounded formulation was then applied to the skin sections (5 mg/cm^2) of the three *ex vivo* human torso skin donors (3 replicates per donor). A receptor solution was placed bathing the inner surface of the skin sections in order to measure the rate of appearance of lorazepam. The percutaneous absorption of the drug was evaluated over a period of 48 hours. During the exposure period, samples of the receptor solutions were removed at pre-selected times (0, 2, 4, 8, 12, 24, 32 and 48 hours) and were analyzed for lorazepam content using the HPLC/UV analytical method. After the last sample of the receptor solutions (collected at 48 hours), the skin sections were washed, tape stripped (to remove the stratum corneum) and separated into the epidermis and dermis to evaluate the skin content of the drug.

Results and Discussion

The total absorption, rate of absorption and the skin content (distribution) of lorazepam was determined for a total of two test formulations containing lorazepam 5 mg/g and propylene glycol 10% (w/w) in Lipoderm and Lipoderm ActiveMax, respectively. The absorption results indicate the percutaneous absorption of lorazepam through the skin whereas the distribution results indicate the percutaneous absorption into the skin. The total absorption and the skin content were determined after 48 hours from a single application of the transdermal compounded formulations in the skin sections. The total absorption corresponded to the total recovered in the receptor solutions and the skin content corresponded to the mass recovered of lorazepam in the stratum corneum, dermis and epidermis (µg/cm^2). The rate of percutaneous absorption, on the other hand, is a time-averaged value and it was determined as the mean flux of lorazepam, collected at the receptor solution under the skin (µg/cm^2/h), over the 48-hour period (Figure 2). The absorption and distribution profiles of lorazepam were similar for both Lipoderm and Lipoderm ActiveMax test formulations (Figure 3). The rate of percutaneous absorption of lorazepam was also similar for both test formulations, though differing in magnitude. The rate of percutaneous absorption showed a slow rise to a peak flux of lorazepam occurring approximately 30 hours after dose application, followed by a slow decline in flux thereafter. Mass accountabilities corresponded to 99% and 104% for the Lipoderm and Lipoderm ActiveMax test formulations, respectively (PCCA, 2013).

Conclusion

Lorazepam - an anxiolytic, sedative, hypnotic and antipsychotic drug - penetrates into and through *ex vivo* human torso skin, following *in vitro* topical application of transdermal compounded formulations. It is concluded that the transdermal bases Lipoderm and Lipoderm ActiveMax may be used in pharmaceutical compounding for the preparation of transdermal compounded formulations.

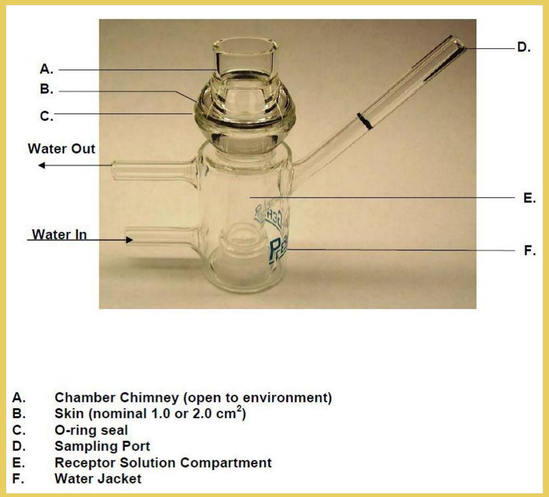

Figure 1. Franz diffusion cell

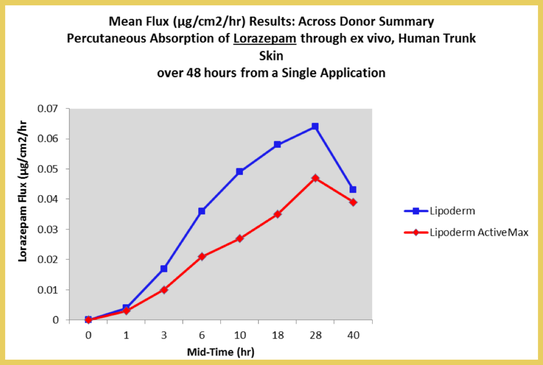

Figure 2. Lorazepam flux versus time

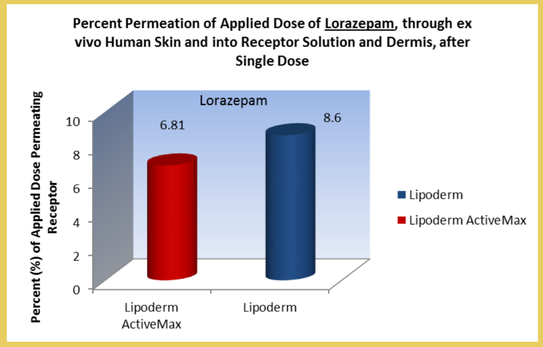

Figure 3. Percent Permeation of Lorazepam

PCCA (2013) Lipoderm. Available at: http://www.pccarx.com/pcca-products/pcca-exclusives/bases/lipoderm (Accessed: 17 July 2014)

Please send correspondence to: PCCAScience@pccarx.com

For a copy of this poster, please scan the QR code