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Significance of High Skin Fluxes Produced By Acyclovir Topical Formulations for Achieving Therapeutic Levels of Drug at the Target Site in the Treatment of Cutaneous HSV-1 Infections in Hairless Mice: A Closer Look at the C* Concept. Phenil J. Patel[1], Abdel-Halim Ghanem[1], William I. Higuchi[1], Jer Hsu[1], V. Srinivasan[2] and Earl R. Kern[3]. [1]Dept. of Pharmaceutics and Pharmaceutical Chemistry, Univ. of Utah, Salt Lake City, UT 84112; [2]TheraTech, Inc., 417 Wakara Way, Salt Lake City, UT 84108; [3]Dept. of Pediatrics, Univ. of Alabama at Birmingham, AL 35294.

For many years, our group has been working on the development of a novel approach for prediction of topical antiviral efficacies of acyclovir (ACV) formulations in the treatment of cutaneous HSV-1 infections in hairless mice. This approach is based on estimation of the free drug concentration (C*), at the target site using the experimentally determined *in vitro* fluxes (J). First, a relationship between ACV flux (using controlled delivery transdermal patches) and efficacy was established by applying a novel method for evaluation of topical and systemic efficacies in hairless mice cutaneously infected with HSV-1 [*Gonsho et al., Int. J. Pharm., 65 (1990) 183-194*]. Then C* for 50% antiviral efficacy (C^*_{50}) was determined from the plasma levels of ACV that inhibited cutaneous lesion formation in 50% of the animals treated systemically [*Imanidis et al., Pharm. Res., 11 (1994) 1035-1041*]. Using this C^*_{50} along with the ACV flux resulting in 50% topical efficacy (J_{50}), the *in vivo* dermis permeability coefficient (P_D) for ACV was estimated using the equation: $P_D = J_{50}/C^*_{50}$. We can then predict efficacy of a topical formulation by calculating C* achieved by the formulation from the experimentally measured flux (J) data using the equation: $C^* = J/P_D$ [*Lee et al., Int. J. Pharm., 93 (1993) 139-152*]. Based on this analysis, it is clear that the formulation which produces a higher skin flux can achieve a higher C*, resulting in a higher predicted efficacy. To further investigate the significance of skin flux, an extensive examination of the C* concept was undertaken using several ACV formulations. For determination of C*, the *in vitro* skin fluxes were measured in an *in vivo-in vitro* experimental design that approximated the *in vivo* antiviral treatment protocol. Then *in vivo* efficacies were measured using the hairless mouse model for cutaneous HSV-1 infections. Our results indicate that over a wide range of efficacies, the predictions based on C* (estimated from the *in vitro* experimental fluxes) are in good agreement with the *in vivo* efficacies. These findings support the validity of the C* concept and underscore the significance of high skin fluxes produced by topical formulations for achievement of therapeutic levels of ACV at the target site. Supported by a Grant-in -Aid from TheraTech, Inc. and by NIH Grant AI20161.

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Lidakol Cream vs Zovirax Ointment for the Treatment of Experimental Dorsal Cutaneous Herpes Simplex Virus Type 1(HSV-1) Infection in the Guinea Pig. M.B.McKeough and S.L.Spruance, University of Utah, Salt Lake City, USA.

Lidakol (10% n-docosanol cream, Lidak Pharmaceuticals, La Jolla, CA) is a 22 carbon-long saturated alcohol which has been reported to be efficacious in the treatment of herpes labialis (*AVR* 1994;23[Suppl.1]:75). To further investigate this new agent, we infected four sites on the backs of 15 female Hartley outbred guinea pigs with HSV-1 by multiple punctures with a vaccination device (Day 0) and evaluated the therapeutic efficacy of topical Lidakol and Zovirax Ointment (5% acyclovir [ACV] ointment, Burroughs Wellcome). ACV was administered 4x/day for 3 days on Days 1-3 and compared with the ointment placebo. Because of skin irritation, Lidakol was given 3x/day for 3 days and compared with untreated control infections. Efficacy was evaluated on Day 4 by assessment of lesion severity and virus titer at each infection site (n=15 for each Rx).

Measure	Lidakol	Untreated	ACV	Control
# of sores	57@	55	56*	58
Area (mm^2)	245	264	177*	245
Virus titer (log_{10}pfu/ml)	5.0	4.9	4.2*	4.9

@, all data are median values; *, p<.01

Zovirax Ointment, a formulation which has been ineffective for herpes labialis, demonstrated a small but significant benefit. Lidakol had no apparent efficacy in this model.