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Qualitative and Quantitative Differences between Intracellular Penciclovir (PCV) Triphosphate (PCVTP) and Acyclovir (ACV) Triphosphate (ACVTP) in a Human Schwannoma Cell Line (SW) Infected With Varicella Zoster Virus (VZV). G.M. Bebault, R.A. Wall, B.A. Rennie, E.M. Smyrnis, and S.L. Sacks. Viridae Clinical Sciences Inc. and University of BC, Vancouver, Canada.

Famciclovir (FCV; Famvir™) is the oral formulation of PCV, a potent and specific antiviral agent which speeds healing and reduces the duration of post-herpetic neuralgia (PHN) in patients with VZV infections. FCV treatment has shown significant therapeutic advantage over both placebo and/or ACV. One suggestion for improved antiviral activity *in vivo* with PCV has been the observation of a prolonged intracellular half-life of PCVTP, suggesting that favorable intracellular pharmacokinetics might maintain antiviral activity at the site of infection even when plasma trough levels fall below the range of activity. Furthermore, since PHN may result from damage to neurons and/or support cells it was of interest to compare the uptake, phosphorylation and intracellular pharmacokinetics of PCV versus ACV in neural support cells. To this end, ACVTP and PCVTP were compared in cytosol extracts of VZV (Ellen)-infected SW treated with ^{3}H-ACV or ^{3}H-PCV, respectively. VZV-infected SW (moi = 0.05 X 3 d at 37°C) were treated X 8 h with 8 μM (PCV) or X 12 h with 9 μM (ACV). SW monolayers were washed X 1 with PBS and extracted with 1.5 mL (50% EtOH, 10% PBS) and concentrated to 500 μL. Antiviral nucleosides and their anabolites were separated using reverse phase ion-pairing high performance liquid chromatography (HPLC), followed by radioactive flow detection. With PCV, the major phosphorylated derivative (86%; 360 pmol/10^6 cells) was PCVTP which had an intracellular half-life of 14 h. In contrast, ACVTP was at the limit of detection (0.5 pmoles/10^6 cells) at the time of drug removal. The higher concentration of PCVTP over ACVTP (>700-fold) would appear to more than compensate for the difference in Ki values for VZV DNA polymerase (1.6 and 0.01 μM, respectively; Littler, et al ICAAC, 1994). We conclude that PCVTP has a prolonged half-life in VZV-infected SW. This may reduce cell damage in both epithelial cells and cells of neuronal origin between doses of FCV. These data support the biochemical rationale for the clinical observation of PHN reduction seen with FCV based on the intracellular persistence of PCVTP.

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A Pharmacokinetic/Pharmacodynamic Approach for the Comparison of Penciclovir and Acyclovir: Utilization of an *in vitro* model which Simulates *in vivo* Pharmacokinetics. F. M. Hamzeh*, H. J. Schaad, P. S. Lietman. Division of Clinical Pharmacology, The Johns Hopkins School of Medicine, Baltimore, Maryland USA.

We have previously described the development and validation of an *in vitro* pharmacokinetic (PK)/pharmacodynamic (PD) system (PK/PD system) in which the drug concentration and the rate of elimination can be manipulated to mimic human pharmacokinetics. We utilized the PK/PD model to study the anti-HSV 2 activity of penciclovir and acyclovir. Initially, both drugs were dosed to infected cells, as a single bolus, to produce C_{max}s of 3, 6, 12, and 24 μg/ml. The drugs were then eliminated with a $T_{1/2}$ of 1.8 h. Infectious virus was detected in the extracellular compartment 24 to 32 h after infection. The time of the appearance of HSV 2 in the medium was dose dependent and drug dependent. Virus titres in acyclovir-treated cultures were 5-20 fold higher than penciclovir-treated cultures 48 h after dosing. We also utilized this system to study the relationship between extracellular pharmacokinetics and the concentration of intracellular phosphates of penciclovir and acyclovir. Using information from clinical studies on the plasma levels of penciclovir from famciclovir, we simulated the pharmacokinetics of penciclovir that occurs after a 500 mg oral dose of famciclovir. The experimental pharmacokinetic parameters (C_{max} 3.06 ±0.01 μg/ml, $T_{1/2}$ 2.27 ±0.08 h, and AUC 9.4 ±0.37 μg.h/ml) in the PK/PD system were comparable to human pharmacokinetics of penciclovir after 500 mg dose of famciclovir (C_{max} 3.3 ±0.57 μg, $T_{1/2}$ 1.93 ±0.5 h, and AUC 7.42 ±1.6 μg.h/ml) (Fowles et al. 1991). Comparable acyclovir levels were simulated in parallel. Penciclovir and acyclovir were washed out of the system with a $T_{1/2}$ of 2.27 h after each dose. After the fourth and last dose, the cells were collected at specified time points for determination of intracellular phosphates of penciclovir and acyclovir. Intracellular acyclovir-triphosphate concentrations at 2 h and 24 h after the last dose were 11.4 and 1.0 pmole/10^6, respectively. The concentration of penciclovir-triphosphate, however, stayed constant (590.2 ±62.7 pmole/10^6 cells) for the 24 h period after the last dose. We conclude that a high steady state intracellular concentration of penciclovir-triphosphate can be achieved with 3 times daily dosing. Acyclovir-triphosphate has a much shorter $T_{1/2}$. The differences in the intracellular kinetics of penciclovir and acyclovir phosphates may have important clinical implications when selecting the best dosing regimen for famciclovir and valaciclovir.