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Use of isotopically chiral [4'-^{13}C] Penciclovir (BRL 39123) and its oral prodrug [4'-^{13}C] Famciclovir (BRL 42810) to determine the absolute configuration of their metabolites. R. A. Vere Hodge, D.L. Earnshaw, R.L. Jarvest and S.A. Readshaw. Smithkline Beecham Pharmaceuticals, Epsom, Surrey, England.

Penciclovir has been shown to have potent activity against HSV-1, HSV-2 and VZV, yet have low toxicity to uninfected cells. Penciclovir, and its oral prodrug famciclovir, are currently in clinical trials. When HSV infected cells were treated with penciclovir, high intracellular concentrations of its triphosphate ester were produced, whereas low or undetectable levels of the triphosphate were formed in uninfected cells. Phosphorylation of one of the hydroxymethyl groups of penciclovir creates a chiral centre. Similarly, famciclovir forms chiral metabolites, during its conversion to penciclovir, when one of the ester groups has been hydrolysed. We have determined the absolute configuration of these metabolites of penciclovir and famciclovir by using isotopically chiral [4'-^{13}C] penciclovir and [4'-^{13}C] famciclovir. Phosphorylation of penciclovir by HSV-1 thymidine kinase gave 75% of the (S) penciclovir monophosphate and 25% of the (R) enantiomer. In HSV-1 infected MRC-5 cells, at least 95% of the penciclovir triphosphate was the (S) enantiomer whereas in HSV-2 infected cells, about 10% of the triphosphate was the (R) enantiomer. During the conversion of famciclovir to penciclovir by an extract of human intestinal wall the esterase(s) removed the acetyl group preferentially (72 to 77%) from the pro-(S) acetoxymethyl group of famciclovir.

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Mode of Action Studies on the Anti-Cytomegalovirus Nucleoside Analog [1-(2-HYDROXY-1-(HYDROXYMETHYL) ETHOXYMETHYL)-CYTOSINE]. C. Talarico, S. Stanat, C. Lambe, J. Tuttle, L. Beauchamp, K. Biron. Burroughs Wellcome Co., Research Triangle Park, NC, U.S.A.

The nucleoside analog [1-(2-HYDROXY-1-(HYDROXYMETHYL) ETHOXYMETHYL)-CYTOSINE] (BW 1117U81) exhibits in vitro activity against human cytomegalovirus, which appears somewhat cell line-dependent. The compound shows only moderate inhibitory activity against varicella zoster virus, but no inhibitory activity against herpes simplex 1 or 2. This nucleoside analog serves as a substrate for the mammalian cell deoxycytidine kinase, as well as the VZV-encoded deoxypyrimidine kinase. Unlike the purine analog ganciclovir, which is preferentially phosphorylated to the triphosphate form in herpes virus-infected cells, this pyrimidine analog is only weakly anabolized in both HCMV-infected cells and uninfected cells. Laboratory selected BW 1117U81-resistant mutants of HCMV are resistant to PFA and HPMPC, indicating an alteration of the DNA polymerase. This suggests that one mechanism of antiviral activity of BW 1117U81 is at the polymerase level.