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Prolonged activity of penciclovir in cell culture against varicella-zoster virus. R. Standring-Cox, T.H. Bacon, B.A. Howard, J. Gilbart and M.R. Boyd. SmithKline Beecham Pharmaceuticals, Great Burgh, Epsom, Surrey, KT18 5XQ, U.K.

Penciclovir (PCV) is a potent and selective inhibitor of varicella-zoster virus (VZV) and herpes simplex virus (HSV-1 and HSV-2) replication in cell culture. The 50% effective concentrations (EC_{50}s) for the sensitivity of clinical isolates of VZV to PCV and acyclovir (ACV) were similar, whether determined by the plaque reduction assay (PCV, 4.4±2.3μg/ml and ACV, 4.5±1.6μg/ml; n=29) or the Hybriwix^{TM} Antiviral Susceptibility Test (PCV, 1.4±0.7μg/ml and ACV, 1.5±0.8μg/ml; n=21) in MRC-5 cells. Both compounds were about 5-fold more active in Hs68 cells than MRC-5 cells based on comparisons of EC_{50}s by the plaque reduction assay. In experiments in which compounds were present continuously, the inhibition of VZV DNA synthesis, as measured by DNA hybridisation, was similar for both compounds. However, the activity of PCV was more prolonged than ACV under conditions where the extracellular compound was withdrawn, by either reducing the treatment time or by treating the cultures with single daily pulses (8 hours) for 5 days. The intracellular half-life for PCV-triphosphate (TP) in MRC-5 cells infected with VZV was much longer than that for ACV-TP, in agreement with results for HSV. The more prolonged activity of PCV in VZV-infected cells treated for a reduced time or intermittently, correlated with the substantially longer intracellular half-life of PCV-TP compared with that of ACV-TP. This prolonged activity of PCV may contribute to the clinical efficacy of the oral form of PCV, famciclovir, in patients with herpes zoster (1); 250mg. famciclovir given three times daily for 7 days was at least as effective as 800mg oral ACV given 5 times daily.

(1) Geeraert, P. et al (The Famciclovir Herpes Zoster Clinical Study Group) (1992). 32nd ICAAC, Anaheim, California, USA, Abstract no. 1108.

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URACIL INCORPORATION INTO THYMIDINE KINASE DEFICIENT VARICELLA-ZOSTER VIRUS DNA

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We isolated a mutant varicella-zoster virus strain(TK$^-$-VZV) which does not induce viral specific thymidine kinase(TK) activity in infected cells. This strain was resistant to 5-bromodeoxyuridine, 5-iododeoxyuridine, *(E)*-5-(2-bromovinyl)-2'-deoxyuridine(BVDU), *(E)*-5-(2-iodovinyl)-2'-deoxyuridine(IVDU), and 1-ß-D-arabinofuranosyl-*E*-5-(2-bromovinyl)uracil(BVaraU) of anti-herpesvirus drugs belong to 5-substituted pyrimidine nucleoside analog. To seek the differences of the nucleotide metabolism between in TK$^+$-VZV(wild type strain)- and TK$^-$-VZV-infected cells, we investigated the uptake and the pathway of pyrimidine nucleosides and its analogs in both VZV-infected cells. Although the uptakes of dThd and anti-herpes virus drugs were little in TK$^-$-VZV-infected cells, dUrd and deoxyuridylate(dUMP) were extremely taken up into TK$^-$-VZV-infected cells. By the trace of [5-^{3}H]dUMP, the replacement of thymine by uracil was proved in TK$^-$-VZV DNA synthesized in TK$^-$-VZV-infected cells. Increase in the intracellular dUTP : dTTP ratio should increase uracil incorporation into VZV DNA in TK$^-$-VZV-infected cells.